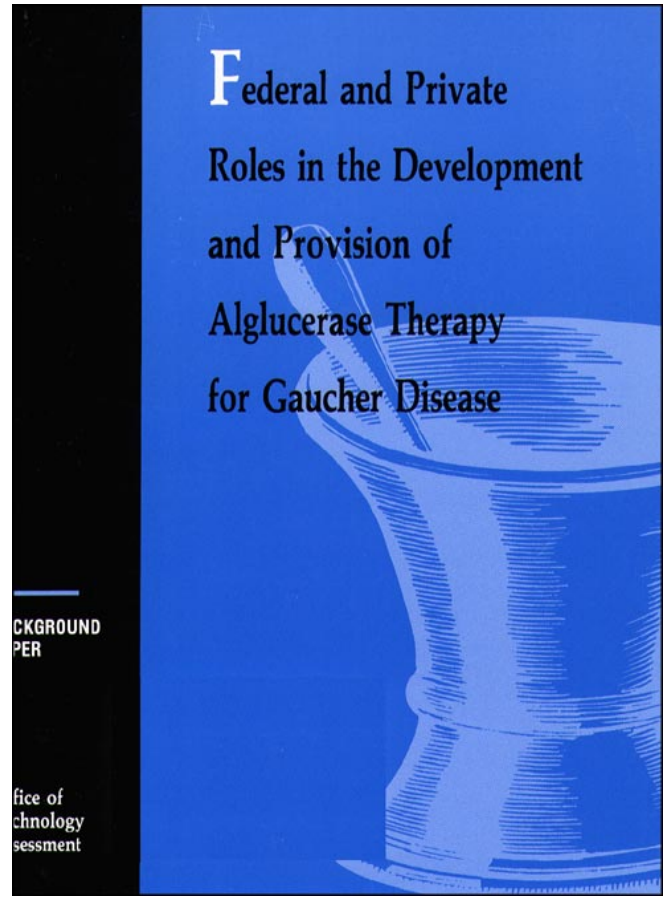
Federal and Private Roles in the Development and Provision of Alglucerase Therapy for Gaucher Disease

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Foreword

The effort to discover and develop new pharmaceuticals is a risky and costly enterprise. For diseases that affect few patients, the barriers to development maybe especially great, since the drugs' small markets may make it difficult for firms to recoup their initial research and development investments. The Federal Government has sought to reduce these barriers through incentives first adopted in the Orphan Drug Act of 1983 (Public Law 97-414). The transfer of technology from Federal laboratories such as the National Institutes of Health to the pharmaceutical industry can also reduce the cost and risk of drug development for firms. Although such incentives may result in important new therapies, their price to patients and insurers may still be high.

As part of our assessment, *Government Policies and Pharmaceutical Research and Development,* requested by the House Committee on Energy and Commerce and its Subcommittee on Health and the Environment and the Subcommittee on Antitrust, Monopolies, and Business Rights of the Senate Committee on the Judiciary, OTA commissioned researchers at Stanford University to examine the development and provision of alglucerase, an important new treatment for Gaucher disease. Gaucher disease is a rare inherited disorder in which the body lacks an enzyme necessary to break down fats. This background paper describes the development of alglucerase, illustrates the role that both the Federal Government and private sector can have in making new therapies available for orphan diseases, and lays out some of the tradeoffs that can exist between developing new medical technologies and controlling health care costs.



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Background Paper

This background paper was prepared as part of OTA's assessment of Government Policies and Pharmaceutical Research and Development.

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Glossary of Abbreviations

BCBS —Blue Cross and Blue Shield
CHAMPUS--Civilian Health and Medical Program of the Uniformed Services
DNA -deoxyribonucleic acid
FDA —Food and Drug Administration
HCFA —Health Care Financing Administration
HCPCS —HCFA's Common Procedure Coding System
HMO —health maintenance organization
IND —Investigational New Drug
NDA —New Drug Application
NIH —National Institutes of Health
ODA -Orphan Drug Act
R&D —research and development
SSA -Social Security Administration

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Federal and Private Roles in the Development and Provision of Alglucerase Therapy for Gaucher Disease

SUMMARY

The drug development and approval process is time-consuming, risky, and potentially costly enough to preclude the development and marketing of treatments for rare disorders. The case of alglucerase, an expensive new therapy for the uncommon inherited disorder called Gaucher disease, illustrates how the Federal Government can help manufacturers overcome critical scientific, financial, and regulatory barriers to the development of such treatments. This paper analyzes public and private investments in the research and development (R&D) of alglucerase. It also examines uncertainty surrounding the appropriate dosing of the drug and the cost implications of alglucerase therapy for patients, their insurers, and the Federal Government.

Gaucher disease is caused by deficient activity of an enzyme necessary to break down glycolipids, substances produced by white blood cells. The accumulation of these glycolipids in the spleen, liver, bone marrow, and other organs can lead to abdominal and bone pain, anemia, and other severe manifestations of disease. Gaucher disease causes significant disability and can be fatal. Between 2,100 and 11,000 people in the United States are believed to have symptoms severe enough to warrant medical intervention.

Alglucerase, marketed under the brand name Ceredase™ by Genzyme, Inc., a Massachusetts pharmaceutical firm, is a chemical derivative of the missing enzyme. Prior to its development, there was no effective treatment for the disease. Although its efficacy has been studied in few patients, existing information suggests that it can reverse some of the symptoms and physical manifestations of the disease.

The** drug was developed **after significant investment** by both the Federal Government and the private **sector. Most of the scientific research that led to the discovery of alglucerase had been sponsored or performed by the U.S. National Institutes of Health (NIH). A critical step was the discovery, by NIH researchers, of the enzyme defect that caused the disease. A second milestone was reached when NIH researchers devised a method for harvesting the enzyme from human placentae, for which they received a patent in 1975. A third milestone was the discovery by NIH researchers of a chemical modification that greatly improved the effectiveness of the enzyme. The modified form became alglucerase.

In addition to the research that took place in NIH's own laboratories, the Federal Government invested almost $1 million in contracts with the New **England** Enzyme Center at the Tufts University Medical School to supply NIH with sufficient quantities of the enzyme to continue the research process. In 1981, Genzyme, then a new firm whose founders included researchers from the New England Enzyme Center, took over the contract to supply the enzyme. ***NIH contracts with Genzyme over the next 11 years totaled nearly $9 million, a figure that represents roughly 20 percent of alglucerase)s measurable R&D costs. This figure does not include the costs of decades of research by talented NIH scientists or the work by researchers at universities and private research institutions whose efforts culminated in alglucerase.***

Because the contributions of NIH included the discovery of alglucerase, Genzyme could not obtain a patent for the drug. Therefore, had it not been for the provisions of the Orphan Drug Act, Genzyme could not be assured of the exclusive rights to market the drug. In 1985, Genzyme's alglucerase received official designation as an orphan drug, entitling the company to 7 years of exclusive marketing, and greatly enhancing the potential profitability of alglucerase.

On the basis of information supplied by Genyzme, we estimate that the firm spent approximately $29.4 million on R&D for placental alglucerase over the decade prior to its approval for marketing in 1991. These expenditures represent cash outlays. They do not account for the time value of the money tied up in the project or for the technical risks of failure along the way. Although Genzyme claims that it spent about $48.6 million in cash outlays, we include only actual expenditures for the work, materials, and facilities needed for the conduct of R&D. The excluded payments are part of the purchase of the valuable asset that Genzyme's

alglucerase had become by the time the firm decided to buy back rights to it from its investors.[1]

In addition to the large public and private investment in the development of alglucerase, further revenues came from Gaucher patients and their insurers. Between 1989 and 1991, patients were able to purchase the then unapproved drug under the U.S. Food and Drug Administration's (FDA) Treatment Investigational New Drug (IND) program. This program provides patients not enrolled in clinical trials with access to experimental drugs for otherwise untreatable conditions. The FDA allowed Genzyme to charge a price to recover costs associated with the R&D and provision of the drug. ***Revenues to Genzyme under the Treatment IND program exceeded $5 million.***

FDA approval of Genzyme's placental alglucerase in April 1991 was based primarily on the clinical experience of 12 patients studied at NIH.[2] Their work indicated that a dose of 60 units/kilogram (kg)[3] administered biweekly for a year resulted in rapid patient improvement. After varying periods of treatment at the initial dosage, researchers elsewhere have successfully decreased the "maintenance' dose that some patients receive to as little as 15 units/kg biweekly. Researchers at the Scripps Institute in California have used an even smaller dose, 2.3 units/kg, administered three times a week. Although patients in these studies had clinical improvements comparable to those of the NIH patients, there is some uncertainty about whether they were as severely ill as patients enrolled in the NIH study.

At ***the range of potential treatment doses studied thus far and the retail price of $3.50/unit, a year of therapy can cost between $71,160 (for 2.3 units/kg thrice*** *weekly) to* $552,760 ***(for 60 units/kg weekly).*** Patients successfully treated with alglucerase will presumably remain on the therapy all their lives (albeit at reduced maintenance doses). According to data supplied by Genzyme, 73 percent of patients on alglucerase in March 1992 had private health insurance that covered their alglucerase therapy, usually with patient out-of-pocket expenses of less than $2,000. Another 21 percent were covered by Medicare or Medicaid.[4] ***Part of the reason for the high price of alglucerase may be its high manufacturing, marketing, and distribution costs, which we estimate to be $1.90/unit in 1992, based on figures supplied by Genzyme.***

Because the vast majority of private health insurance policies impose a limit on total benefits payable for each insuree, ***somewhere between one-third and one-half of all alglucerase recipients face a significant risk of exhausting or critically reducing their available insurance benefits over time.*** Although Genzyme supplies the drug free to those patients who exhaust (or otherwise lack) insurance benefits, for the rest of their lives such patients remain uninsured for the cost of administering alglucerase and ***any other medical expenses they may incur.***

Genzyme's pricing arrangement means that insurers are typically obligated by contract to pay most[5] of the drug's price for all FDA approved indications; patients without insurance or other resources, who would often forgo therapy rather than pay the full price, pay nothing for the drug. Although the company gains no revenue on each unit of drug offered free of charge, the overall pricing strategy can be profitable. ***Genzyme's pricing is similar in its consequences to a policy in which patients are offered a lifetime supply of alglucerase in exchange for the value of their remaining insurance coverage and associated copayments.***

The drug's high cost to consumers, private insurers, and the Federal Government raises questions about the extent to which NIH is acting in the public interest in providing significant assistance to some medical technologies ultimately marketed by the private sector. The actions of NIH can have consequences far beyond providing new therapies to combat disease. ***As is illustrated by this case, such deep involvement creates the potential for the***

1 In exchange for funds to develop alglucerase, Genzyme had transferred rights to the drug in 1987 to a limited partnership. Genzyme was the managing partner of the limited partnership.

2 Genzyme is currently conducting clinical research using a recombinant form of the enzyme that it hopes will replace the placental form.

3 One kilogram equals 2.206 pounds.

4 Although Medicare pays only 80 percent of therapy, the cost of therapy, the vast majority of these patients have supplement private insurance that pays at least some portion of the remaining 20 percent. Medicare patients without such supplemental insurance are liable for the 20 percent copayment which can reach tens of thousands of dollars. Medicaid pays virtually all of the costs of alglucerase therapy.

5 Insured patients typically are obligated to pay a copayment and deductible out-of-pocket for insured medicines and services.

Federal Government to pay for such technologies twice-once through support of the R&D process and once again as a health insurer. The Federal Government has no mechanism to ensure that the prices Americans pay for drugs and other technologies reflect the public's contribution to their development.

INTRODUCTION

The drug development and approval process is time-consuming and potentially costly enough to preclude the development and marketing of treatments for rare disorders. The Federal Government can help potential manufacturers overcome critical scientific, financial, and regulatory barriers to the development of such treatments. Many Federal laboratories, especially those at NIH, conduct drug discovery research or develop other vital technology for the treatment of disease. The availability of this technology and Federal assistance in its transfer to the private sector can significantly reduce the cost to a manufacturer of conducting drug R&D. Government-sponsored research can also reduce the risk that the manufacturer's efforts to develop a drug will fail by conducting or sponsoring research that helps establish approaches to the treatment of a disease that are likely to be safe and effective.

Pharmaceutical regulation, so often seen as a barrier to innovation, is another means by which the Federal Government can help make the development of new drugs profitable. The Orphan Drug Act (ODA) (Public Law 97-414), enacted in 1983, is an example of a set of pharmaceutical regulations designed to promote, not impede, the marketing of new drugs. The act offers firms incentives to develop treatments for rare disorders. These incentives include research grants, investment tax credits, assistance in negotiating the approval process, and, most importantly, exclusive license to market the product for a specific indication for 7 years. Drug manufacturers can already exclude other producers by obtaining patent protection for their products, but the period of exclusivity under the ODA does not begin until the drug receives final approval from the FDA; as a result, the ODA may extend market exclusivity after the patent has expired. Furthermore, the ODA can confer market exclusivity even when a patent is not or cannot be awarded.

Both types of Federal involvement were vital to the development of alglucerase, a new and expensive drug for Gaucher disease. Gaucher disease is a serious but rare genetic disorder that results from insufficient activity of the enzyme glucocerebrosidase. Government-sponsored research conducted from the mid 1970s to the early 1980s led to the discovery of alglucerase, an apparently efficacious chemical derivative of the missing enzyme. To translate these scientific breakthroughs into better patient care required large-scale production of alglucerase, which could only occur as part of its commercial development. Commercial development, in turn, built upon the scientific discoveries that led to the discovery of alglucerase and it required the expectation that the enterprise would be profitable. Product development might not have proceeded as quickly, if it proceeded at all, without orphan designation.

In this paper, we describe the development of Ceredase™, a brand of alglucerase marketed by Genzyme, Inc. of Massachusetts, and the roles of the Federal Government in this process. We then focus on the provision of this drug-its availability and its cost implications for patients, the Federal Government, and private health insurance. The case of alglucerase dramatically illustrates the challenges that Americans face in devising policies to control health care costs without deterring the development of efficacious new technologies.

DESCRIPTION OF GAUCHER DISEASE

Gaucher disease is an inherited metabolic disorder characterized by the accumulation of compounds called glycolipids, substances ordinarily broken down by the enzyme glucocerebrosidase (8,18,19,20, 33,78). A set of genetic defects in Gaucher patients causes decreased activity or absence of this enzyme. Consequently, glycolipids, which are primarily derived from white blood cells, accumulate in the spleen, liver, bone marrow, and other organs. The clinical manifestations of glycolipid deposition include abdominal enlargement, low blood counts, and severe bone pain. Less frequently, the glycolipids can accumulate in the brain, lungs, heart, kidney, and skin.

Forms of the Disease

The clinical severity of Gaucher disease varies dramatically, but the severity may not be closely associated with the specific genetic defect. Several

genetic mutations cause this enzyme deficiency (22,26,51,63,75,80,1 10,111) but, according to several researchers, the same mutation may lead to heterogeneous disease presentations, and patients with similar clinical manifestations do not necessarily have the same genetic abnormality (8). Other researchers claim that there is a strong association between genetic abnormality and disease severity (20,22,26,61,108,124). As a group, these studies suggest that there is a link between the two characteristics, but the strength of this link may be influenced by environmental conditions and other unknown genetic factors.

Gaucher disease is classified into three categories based on its clinical presentation. Type 1, the adult form, is usually the least severe. Although the name suggests that this condition is present only in adults, it may manifest itself at any time. Its presentation is very heterogeneous; some patients may be asymptomatic or have only minimal symptoms, while others may suffer severe and chronic life-long disability. This chronic condition affects the spleen, liver, and bone marrow. The enlarged spleen is thought to accumulate and destroy platelets and red and white blood cells. The bone marrow, the normal site of production of blood cells, maybe unable to replace the destroyed cells because it is also infiltrated with glycolipid. The patient consequently develops anemia, resulting in fatigue and shortness of breath. A low platelet count causes excessive bruising and bleeding. The macrophages, cells which eliminate debris and other contaminants from the blood and other tissues, become congested with unmetabolized glycolipids and restrict blood flow to the bones, thereby decreasing the oxygen supply and causing the bone pain experienced by many Gaucher patients. This pain can be debilitating, resulting in frequent confinement to bed. The bones are also more likely to deteriorate and fracture, sometimes leading to deformities that restrict the patient to a wheelchair. Although rare, breathing problems can be severe enough to warrant oxygen therapy. Child development can be affected as well; the onset of puberty may be delayed, and the growth of teeth and bones may be impaired. It was thought that Type 1 disease tended to follow a progressive downhill course, but some investigators now believe that when these patients reach early adulthood, the disease course stabilizes (20).

Four genetic mutations are responsible for about 97 percent of the cases of Type 1 Gaucher disease in the Ashkenazi Jewish population (22,25,26). Three of these abnormalities, designated by geneticists as 1226, 1448, and IVS2+1 result from a single substitution within the patients DNA (deoxyribonucleic acid). The fourth, 84GG, is due to an insertion in the DNA template. The 1226 mutation accounts for 77 percent of the genetic mutations in the Ashkenazi Jewish population but for only 25 percent of the cases in non-Jews. It is thought to cause a less severe form of the disease. The 84GG mutation causes about 13 percent of the genetic abnormalities in the Jewish population and much less in the non-Jewish segment. The IVS2+1 mutation, which was very recently described, accounts for about 2.5 percent of the mutations in Jews and a much smaller percentage in non-Jews. Persons with the 84GG and IVS2+1 mutations do not produce the enzyme and have severe forms of Gaucher disease. The 1448 abnormality, which is thought to be responsible for more serious disease and for brain involvement, occurs in about 40 percent of the non-Jewish Gaucher population but in only 3 percent of the Jewish Gaucher patients. These four genetic defects account for only about 65 to 75 percent of the cases of Gaucher disease in the non-Jewish population. Remaining mutations are either unidentified or sporadic and restricted to a few families (51,63,80).

Type 2, the infantile form, is the most severe of the 3 types. It usually becomes apparent before 6 months of age and is fatal within 2 years. Central nervous system involvement distinguishes this form of the disease from Type 1. Infants with Type 2 disease have abnormal movements and postures, along with difficulty handling oral secretions, and seizures.

Type 3, the juvenile form, is of intermediate severity. Its manifestations are similar to those of Type 2, and include abnormal eye movements, seizures, and dementia, but it involves the neurological system later in its course.

Prevalence

The prevalence of each type of Gaucher disease depends on both its incidence (rate of new cases per year) and the longevity of patients. The most common form is Type 1, which affects Ashkenazi Jews at a greater rate than the general population. The other two types are rare; they appear to affect no more than one of 50,000 births (8). The incidence of Type 3 disease is greater among people from the province of Norrbotten in Sweden than the popula-

tion as a whole. Type 2 does not have an apparent ethnic predilection.

The specific prevalence of each form of the disease is uncertain. Most estimates of disease prevalence are based on the frequency of the disease genes in the population, a rate which itself is uncertain. Prior to the recent advent of genetic technology, estimates of the incidence of Gaucher disease were imprecise. Thus, as table 1 shows, there was a wide range of estimates of disease incidence. These estimates were initially based on the actual number of Gaucher patients within a sample of the Ashkenazi Jewish population. Later estimates were based on detection of carriers using an assay to assess glucocerebrosidase activity, but because there is considerable overlap in the level of enzyme activity between normal individuals and carriers of Gaucher disease, the assay does not reliably identify carriers (29). After the precise genetic abnormalities causing Gaucher disease were discovered, it became possible to detect the disease more accurately with a blood test and to determine the gene frequency and birth incidence with much greater precision. The genetic tests have been more useful in Jewish than in non-Jewish populations, since the genetic mutations causing the disease are better characterized in the Ashkenazi Jewish population.

Between about 6.6 and 10 percent (1/15 to 1/10) of the Ashkenazi Jewish population are believed to carry a form of the abnormal genes that cause Gaucher disease (20,21,25,123). Disease develops only in persons who have two such mutations. On average, this occurs in one-quarter of the offspring of pairs of carriers of Gaucher disease. If Ashkenazi Jews only married other Ashkenazi Jews, i.e., there were 100 percent intramarriage within the Ashkenazi Jewish population, then the birth incidence of the disease would be between 1/1,000 and 1/400 within this population. If these assumptions are valid, and affected patients do not have shortened life spans, among the 6 million Jewish people in the United States there are between 6,000 and 15,000 with Gaucher disease. Insofar as Gaucher patients have higher mortality rates than the general population and the intramarriage rate is less than 100 percent, the actual prevalence of the disease maybe lower.

Limited data suggest that there are as many non-Jews as Jews with Type 1 disease in the United States (21). Estimates of the birth incidence of the disease in the United States are listed in table 1. Jewish people tend to have a genetic mutation that results in a less severe form of the disease. By one estimate, only about 10 to 20 percent of Ashkenazi Jews with the disease warrant medical intervention (21). In contrast, of the estimated 10,000 non-Jews with the disease, about 60 to 80 percent may be sufficiently symptomatic to require therapy (21), implying that about 2,100 to 11,000 Gaucher patients in the United States would be candidates for medical intervention. Genzyme, Inc., the manufacturer of alglucerase, has suggested that only 3,000 Type 1 Gaucher patients in the United States (50 percent of them Jewish) have severe enough disease to warrant treatment, although there may be as many as 3,000 moderate to severely affected patients outside of the

Table I—Incidence of Gaucher Disease in the United States

	Incidence		Absolute number affected		Number warranting enzyme replacement therapy	
Disease type	Jews	Non-Jews	Jews	Non-Jews	Jews	Non-Jews
1	1 :400-1 :1,000	1 :25,000-1 :100,000	6,000-15,000	2,500-10,000	600-3,000	1,500-8,000
2	1:40,000-1:100,000	1:40,000-1:100,000	60-150	2,500-6,250	NA[a]	NA[a]
3	1:40,000-1 :100,000	1 :40,000-1 :100,000	60-150	2.500-6.250	NA[a]	NA[a]

[a]It is not yet known if Type 3 will be amenable to enzyme replacement therapy. Recent data suggest that it may be (1 8). Type 2 Currently is not amenable to enzyme replacement therapy.

SOURCES: J.A. Barranger and El. Ginns, "Glucosylceramide Lipidosis: Gaucher Disease," *The Metabolic Basis of Inherited Disease,* 6th Ed., C.R. Scriver, A.L. Beaudet, W.S. Sly, and D. Valle (ads.) (New York, NY: McGraw-Hill, 1989); E. Beutler, "Gaucher's Disease," *New England Journal of Medicine* 325:1354-1360, 1991; E. Beutler, T. Gelbert, W. Kuhl, et al., "identification of the Second Common Jewish Gaucher Disease Mutation Makes Possible Population-Based Screening for the Heterozygous State," *Proceedings of the National Academy of Sciences USA* 88:10544-10547, 1991; Y. Matoth, S. Chazan, A. Cnaan, et al., "Frequency of Carriers of Chronic (Type 1) Gaucher Disease in Ashkenazi Jews," *American Journal of Medical Genetics* 27:561-565, *1987;* E. Beutler, Chairman, Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA; A. Taunton-Rigby, Senior Vice-President, Bio-Therapeutics, Henri Termeer, Chief Executive Officer and David McLachlan, Senior Vice President and Chief Financial Officer, Genzyme, Boston, MA, personal communications, February 26, 1992; A. Taunton-Rigby, personal communication, June 12, 1992; A. Zimran, T. Gelbert, B. Westwood, et al., "High Frequency of the Common Jewish Mutation for Type 1 Gaucher Disease Among the Ashkenazi Jewish Population," *Blood* 76:199a, 1990; A. Zimran, T. Gelbart, B. Westwood, et al., "High Frequency of the Gaucher Disease Mutation at Nucleotide 1226 Among Ashkenazi Jews," *American Journal of* Human *Genetics* 49:855-859, 1991.

United States (107,107a). As described later in this paper, clinical researchers are currently investigating the potential of alglucerase to benefit less severely affected patients (10) and sufferers of Type 3 disease (21), as well as to provide prophylaxis to asymptomatic patients whose disease might otherwise become symptomatic (32,61). The results of this research could lead to a growth in the potential market for alglucerase.

Diagnosis

The disease is diagnosed by documenting the enzyme deficiency in various tissue sources. White blood cells, which can be obtained from a sample of blood drawn from a vein, provide a convenient and reliable specimen. People with the disease have substantially less enzyme activity than normal subjects, and thus there is no overlap between the two groups. Measuring enzyme levels is not a reliable test for the detection of carriers (i.e., people with one abnormal gene) since their level of enzyme activity is similar to that of normal people. Although assessment of the level of enzyme activity has been established as a useful and dependable test for the diagnosis of Gaucher disease, some physicians still resort to bone marrow examination. This is a more painful, time-consuming, and costly procedure. It requires removing a sample of the patient's bone marrow either from the hip or sternum with a specially designed needle and examining the marrow for the presence of certain cells that are characteristic of Gaucher disease. Bone marrow testing is imperfectly sensitive, since the abnormal cells are not distributed uniformly throughout the marrow and may be absent from one or more samples. In addition, cells found in other abnormalities may mimic these "Gaucher cells, " leading to a false-positive diagnosis (29).

Genetic analysis has improved detection of carriers, facilitating prenatal counseling and diagnosis (25,26). Since 95 percent of the genetic mutations causing Gaucher disease in the Ashkenazi Jewish population can now be easily identified (i.e., 1226, 1448, 84GG[6]), there is only 1 chance in about 1 million that a Jewish couple in which one of these three genetic defects is not found would be at risk for having a child with Gaucher disease. This risk decreases to about 1 in 1.6 million if both members of the couple are examined for all the genetic mutations currently known to cause Gaucher disease. If one but not the other parent has one of these three mutations, the risk is 1 in 1,000 that they will have a child with Gaucher disease (25). If a parent is a carrier of a Gaucher gene and the other parent tests negative for these three mutations plus all currently discovered genetic defects, this risk would fall to 1 in 1,300. For the non-Jewish population, carrier testing is less sensitive because only 65 to 75 percent of the genetic defects responsible for the disease have been characterized.

DNA analysis can be supplemented by measurement of enzyme activity in the potential parent. If the enzyme level is normal, it is even less likely that a subject who has no genetic abnormality will be a carrier. However, this method does not completely exclude carrier states since, as previously mentioned, the enzyme levels of normal people and carriers can overlap significantly.

If both members of a couple are known to be carriers of Gaucher disease, the likelihood that their child will have the disease is one in four. Prenatal diagnosis can be performed through determination of the fetus's enzyme levels and DNA analysis of cells cultured from the mother's amniotic fluid. Those researchers who claim that there is a strong correlation between genetic abnormality and clinical severity believe that genetic analysis of the fetus will enable them to advise the parents on potential disease course.

Treatment

Prior to the introduction of enzyme replacement therapy, the goal of medical care was amelioration of the symptoms of the disease. Physicians sometimes recommended splenectomy, surgical removal of the spleen, either because they believed that it had enlarged enough to cause symptoms directly, or it had trapped enough platelets to depress the platelet count. Splenectomy is now reserved for unusually severe symptoms, because removal of the spleen increases the risk of infection, and because unmetabolized glycolipid may accumulate more rapidly in other organs after the spleen is removed. The anemia of Gaucher disease has been treated with blood transfusions; the bone pain with pain medica-

6 The recently discovered IVS2+1 mutation mentioned earlier explains an additional 2 to 3 percent of genetic mutations causing Gaucher disease in the Ashkenazi Jewish population. It is not yet known how this mutation alters the statistics on risk of Gaucher disease presented in this section.

tions, oxygen therapy, and bed rest; and other skeletal problems with surgery.

Treatment of the underlying enzyme deficiency was formerly a difficult and risky procedure. Until the development of enzyme replacement therapy, the only form of treatment that actually corrected the underlying disorder was bone marrow transplantation, a process in which the cells of a patient's bone marrow are destroyed by radiation and chemotherapy and replaced by marrow from a normal donor (50,71,74,78,79,81,99,105,109). Because the cellular elements of the transplanted marrow contain a normal gene for glucocerebrosidase, transplantation should enable the patient to produce cells that contain normal levels of the enzyme. This procedure requires a genetically matched donor, and even then it remains a potentially lethal treatment for a frequently nonlethal condition. Fewer than 20 such procedures have been performed successfully. Hopes that transplanted spleens and kidneys would similarly serve as a permanent source of the enzyme proved fruitless (66,67).

ENZYME REPLACEMENT THERAPY

The lack of success of these therapies for Gaucher disease led to further efforts to replace the missing enzyme. Since the mid 1970s, investigators at a number of institutions had been attempting to extract glucocerebrosidase from human tissue. Researchers at the NIH and Scripps Clinic independently developed methods to harvest the enzyme from human placental tissue (44,96). In 1975, a patent was issued to two NIH researchers for their method (Application no. 451,300). However, initial efforts to treat at least 18 patients with the enzyme were unsuccessful. Investigators were unable to produce sufficient quantities to administer adequate doses, and it became clear that the native enzyme would need to be modified in order to ensure adequate absorption by the cells in the body needing it most (17,23, 24,34,35,37,64).

During the early 1980s, researchers made significant progress toward overcoming these obstacles (2,39,45,48,56,57,62,88,90,94,104,106). After devising a more efficient placental harvesting procedure, they developed a modified form of the enzyme that was preferentially absorbed by macrophages, the cells that utilize the enzyme to break down glycolipids. They also designed a more effective dosage protocol (14). Alglucerase infusions were found to have therapeutic potential in the treatment of Type 1 disease. Even now, it is not known whether this treatment influences the forms of Gaucher disease that affect the nervous system.

There is a great deal of controversy about the best treatment regimen to use. It is very difficult to distinguish the efficacy of alternative regimens because there are no direct comparisons of the regimens in randomized clinical trials. Furthermore, it is difficult to ascertain whether the patient populations in different studies are truly comparable. Finally, in part because Gaucher disease is an uncommon condition, the number of patients in many of the studies is too small to confer adequate statistical power.

Mode of Administration

The modified enzyme is packaged as a liquid in a 5-milliliter (ml) vial containing 400 units or 80 units/ml. Before patient administration, the concentrated form of the enzyme is diluted with a saline solution to 100 ml (4 units/ml). Ordinarily the drug can be administered on an outpatient basis by a nurse. An intravenous line is started, usually in the forearm, and each patient is given a 5-ml test dose and observed for 10 minutes. If no adverse reaction is noted, the remainder of the predetermined dose is administered over a 1-to 2-hour period. If the patient does not experience any ill feelings during this interval, he or she leaves shortly after the infusion is completed.

Clinical Experience

NIH, Scripps Clinic, and Mount Sinai Medical Center have the greatest clinical experience with alglucerase. Each has pursued somewhat divergent dosing strategies. This section reviews the clinical experience of each institute chronologically. Following the presentation of this evidence, conclusions are drawn regarding the efficacy of various treatment strategies.

Clinical experience with chemically modified enzyme actually began in 1983 at the NIH, but much of this early work is unpublished. The FDA considered NIH data in its regulatory review of alglucerase, along with data from Genzyme acquired during the IND (Investigational New Drug) phase. The existing clinical experience with alglucerase is summarized in table 2.

Table 2—Clinical Experience With Ceredase

Institution	Date	Number of patients	Dosage regimen
NIH	1983	8	2-12 units/kg weekly
NIH	1983-present	1	30 units/kg weekly and biweekly (high-dose unfractionated)
NIH	1986-1988	23	0.6-234units/kg single dose
NIH	1989-present	12	60 units/kg weekly and biweekly for 2 years; decreased to 30 units/kg for 6 months (high-dose unfractionated) and then further reduced to 15 units/kg
NIH	Fall 1991-present	40	IO units/kg biweekly (low-dose unfractionated)
Scripps	1990-present	20	2.3units/kg 3 to 7 times weekly (low-dose fractionated)
Shaare Zedek Medical Center,Israel	1991-present	10	2.3 units/kg biweekly
Mount Sinai Medical Center, New York...	1990-present	41	7.5-60 units/kg biweekly
Albert Einstein College of Medicine	1990-present	1	60 units/kg biweeldy
University of Pittsburgh	1990-present	1	60 units/kg biweekly
Universityof NewMexico	1990-present	1	60 units/kg biweekly

SOURCES: N. Barton, "Ceredase (Microphage-Targeted Glucocerebrosidase) for the Treatment of Type 1 Gaucher's Disease," *Proceedings From the Endocrinologic and Metabolic Advisory Committee* 1 :135-248, 1990; N.W. Barton, F.S. Furbish, G.J. Murray, et al., "Therapeutic Response to Intravenous Infusions of Glucocerebrosidase in a Patient With Gaucher Disease," *Proceedings of the National Academy of Sciences USA 87:1913-1916, 1990;* N.W. Barton, R.O. Brady, J.M. Dambrosia, et al., "Dose-Dependent Responses to Microphage-Targeted Glucocerebrosidase in a Child With Gaucher Disease," *Journal of Pediatrics 120:277-280, 1992;* N.W. Barton, G.J. Murray, and R.O. Brady, "Hematological Responses Are Dependent on the Amount of Glucocerebrosidase Administered to Patients With Gaucher's Disease," Blood 78:431a, 1991; N.W. Barton, R.O. Brady, J.M. Dambrosia, et al., "Replacement Therapy for Inherited Enzyme Deficiency-Microphage Targeted Glucocerebrosidase for Gaucher's Disease," New *EnglandJournalofMedicine 324:1* 464-1470, 1991; N. Barton, Chief, Clinical Investigation Section, Developmental and Metabolic Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, personal communication, January 21, 1992; E. Beutler, "Gaucher's Disease," *New EnglandJoumalof Medicine 325:1354-1360, 1991;* E. Beutler, A. Kay, A. Saven, et al., letter, *New Journal of Medicine 325:1809-1810, 1991;* E. Beutler, A. Kay, A. Saven, et al., "Enzyme Replacement Therapy for Gaucher Disease," Blood78:l 183-1190, 1991; E. Beutler, Chairman, Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA, personal communication, February 26, 1992;A. Zimran, I. Hadas-Halpern, and A. Abrahamov, letter, *New EnglandJournal of Medicine 325:181 O-1811, 1991; G.* Grabowski, Professor, Department of Genetics and Molecular Biology, Mount Sinai Medical Center, New York, NY, personal communication, January 28, 1992; S. Fallet, M.E. Grace, A. Sibille, et al., "Enzyme Augmentation in Moderate to Life-Threatening Gaucher Disease," *Pediatric Research 31:496-502, 1992;* H.M. Nitkowsky, A. Madan, and H. Goldman, "Experience With Intravenous Infusions of Glucocerebrosidase in a Patient With Gaucher Disease," abstract #560, *American Journal of Human Genetics,* vol. 49, 1991; T. Ohashi, S. Marchese, D. Pegram, and J.A. Barranger, "Development and Application of a Treatment for Gaucher Disease Using Glucocerebrosidase Targeted to Macrophages," abstract #552, *American Journal of Human Genetics, vol. 49,* 1991; T.J. Gribble and K. Latimer, "Successful Use of Enzyme Therapy in Gaucher's Disease," abstract #556, *American Journal of Human Genetics,* vol. 49, 1991; R.O. Brady, J.M. Dambrosia, and N.W. Barton, "Effectiveness of Low-Dose Replacement Therapy in Gaucher's Disease," *Clinical Research 40:144A,* 1992; M.L. Figueroa, Y. Sate, A. Kay, and E. Beutler, "Efficacy of Frequently Administered Microphage-Targeted Glucocerebrosidase in the Treatment of Gaucher Disease," *Clinical Research 40:167A,* 1992; A. Abrahamov, 1. Hadas-Halpern, E. Levy-Lahad, and A. Zimran, "Enzyme Replacement Therapy for Children With Gaucher Disease: Low Dose, High Frequency, Lower Cost, High Efficacy,'*Pediatric Research 31 :137A, 1992; G.M.* Pastores, A.R. Sibille, and G.A. Grabowski, "Enzyme Augmentation Therapy in Gaucher Disease Type 1: Dosage, Efficacy and Adverse Effects," *Clinical* Research 40:357A, 1992.

The National Institutes of Health

NIH's first efforts (during the early 1980s) with the microphage-tmgeted alglucerase involved eight patients. These participants received a freed weekly dose of 189 units (9). Only one of these patients, the smallest, showed any clinical improvement. His allotment was equivalent to a dose of 9-12 units/kg, the highest in the study (10). Since that time, he has continued to receive enzyme replacement therapy with weekly to biweekly doses of 30 units/kg (9). His blood counts improved, the size of his spleen and liver decreased, and his bone is rebuilding. Although the patient had a more marked response to the higher dosage of enzyme, he did respond at the lower doses. The red blood cell count initially rose 11/2 times more rapidly with the high dose than with the low-dose regimen. On the low-dose regimen, the red cell count improved, but did not normalize (12,15).

To refine the dosage regimen, NIH researchers tested the responses of 23 patients to the administration of single doses of alglucerase. The doses ranged from 0.6 to 234 units/kg. They measured plasma levels of the enzyme during the infusion, then estimated their clearance from the bloodstream after the infusion was stopped (15). Forty-four hours later, NIH researchers performed a liver biopsy in 21 of these patients (9).

From the lowest dose up to approximately 100 units/kg of body weight, the plasma concentration of the enzyme increased in proportion to the amount of enzyme infused. Beyond this dose, there was no further rise in its plasma concentration, suggesting

that the enzyme receptors (the sites on the macrophage that actually absorb the enzyme) were saturated. Thus, doses beyond 100 units/kg appear not to be efficiently utilized by the body.

Liver glucocerebroside levels decreased in 8 of 11 patients who received greater than 30 units/kg, whereas it decreased in only 1 of 10 patients who received a lower dose. However, 6 of these 10 low-dose patients had some apparent diminution in glucocerebroside storage deposits in the liver by electron microscopy.

Interpreting these findings to mean that a minimum dose of 30 units/kg was required for initial therapy, NIH investigators enrolled four adults and eight children with moderate to severe Type 1 Gaucher disease in a study of a higher dosage regimen (11,89). This is the only case series the NIH has published about its clinical experience with alglucerase. Upon entry into the study, all patients were anemic, had enlarged livers and spleens, and displayed evidence of bone abnormalities on x-rays. Study participants received 60 units/kg of alglucerase administered intravenously every 2 weeks. Two severely affected patients received twice that dosage in weekly alglucerase infusions of 60 units/kg. After 9 to 12 months of therapy, all participants experienced improvement and none suffered signifi cant toxicity. The red blood cell count increased significantly in all 12 patients and the platelet count increased significantly in seven patients. The spleen size decreased significantly in all patients and the liver in five. Bone pain responded less dramatically. All recipients felt that their quality of life had improved as a result of the enzyme replacement therapy. In a comparison with 12 untreated Gaucher patients, all adults with less severe disease, the treated group performed more favorably. However, this comparison group cannot be considered a control group in any conventional sense, because there was no attempt to match patients in any fashion.

The dose of 60 units/kg biweekly was continued in these 12 patients for a second year. NIH researchers (10) observed that the maximum hematological response occurred after 9 to 12 months of enzyme replacement therapy and then plateaued. The greatest decline in liver and spleen size seemed to occur later; after 18 months there was a 55 percent decrease in splenic size. On the basis of the response of a child they began treating in 1983, NIH researchers believe that significant skeletal improvements do not develop until after at least 3 years of therapy. After 2 years on the therapy, the dose was decreased to 30 units/kg biweekly for 6 months and then further reduced to 15 units/kg biweekly. After 4 months at this dosage (July 1992), the clinical status of the patients had not deteriorated. The researchers expect to reduce the dosage further to 7.5 units/kg biweekly in September 1992, with further reductions planned, dependent on the clinical well-being of the patients (10).

NIH has two experiences with lower dose therapy (10). One is a single case of a patient whose dose was decreased from 60 units/kg biweekly to 7.5 units/kg biweekly. He continued to show improvement, albeit modest, on the lower doses. In the other case, NIH is conducting a two-anneal trial involving less severely ill patients than the previously described study. Each arm enrolled 20 patients, none of whom had undergone splenectomy. The researchers initiated enzyme therapy in both groups using 10 units/kg biweekly. One group was also given a vitamin designed to enhance the uptake of the enzyme by increasing the number of microphage receptors. Of the 12 patients for whom preliminary results are available (it is not yet known from which arm they originated), 8 had significant improvement in their red blood cell count, and 3 of them experienced a reduction in spleen size after 6 months of therapy (36). These data imply that treatment can be initiated at lower doses of enzyme in clinically stable patients without immediately threatening medical problems (10). Table 3 summarizes the data on the efficacy of low-dose (unfractionated) therapy.

Scripps Clinic

Researchers at Scripps Clinic have reported administering alglucerase to 11 patients with moderate to severe[7] Type 1 Gaucher disease for 3 to 24 months (20,27,28,53). They utilized only one-quarter of the total dose recommended by NIH (30 units/kg every 4 weeks), but gave it 3 times weekly. Their rationale for a frequent (or fractionated) low-dose therapy rests on the hypothesis that there are two types of receptors on human macrophages for glucocerebro-

7 Researchers at NIH have claimed that because some of the patients at Scripps do not have a spleen, the amount of glycolipid deposits may be less than that of patients at NIH and thus the two patient populations may not be comparable.

Table 3-Clinical and Experimental Evidence Supporting Low-Dose Therapy Unfractionated[a]

Institution	Year	Experience
NIH	1983-present	Single patient had some improvement in his hemoglobin at doses as low as 9-12 units/kg.
NIH	1986-1988	23 patients received a single infusion of the enzyme in doses ranging between 0.6-234 units/kg. Although only 1/10 of the patients receiving less than 30 units/kg had a decrease in liver glucocerebroside, 6/10 had structural changes in hepatic storage deposits.
NIH	1991-present	12 patients who received at least 2 years of enzyme therapy with 60 units/kg biweekly were decreased to 30 units/kg biweekly for 6 months and their hematological response was stable. Currently they receive 15 units/kg, and after 4 months on this dose, their clinical status has not deteriorated.
NIH	1990-present	Single patient was decreased from 60 units/kg biweekly to 7.5 units/kg biweekly. There was a modest but milder improvement observed at the lower dose.
NIH	1991-present	40 patients are receiving 10 units/kg biweekly; and 20 of these are also receiving a therapy designed to enhance the uptake of the enzyme. Preliminary data suggest both groups are responsive.
Mount Sinai Medical Center, New York	1990-present	41 patients are being treated with doses between 7.5 and 60 units/kg biweekly. The observed clinical responses do not appear to be dose dependent.
Genzyme's international Collaborative Gaucher Group	1992	Approximately 75 patients throughout the country received initial doses lower than 60 units/kg biweekly. They demonstrate increased red blood cell counts and decreased organ volume after 1 to 3 months of therapy.

a Unfractionated refers to low-dose therapy being given biweekly rather than three times weekly.

SOURCES: N. Barton, "Ceredase (Microphage-Targeted Glucocerebrosidase) for the Treatment of Type 1 Gaucher's Disease," *Proceedings From the* Endocrinologic and Metabolic Advisory Committee 1 :135-248, 1990; N.W. Barton, F.S. Furbish, G.J. Murray, et al., "Therapeutic Response to Intravenous Infusions of Glucocerebrosidase in a Patient With Gaucher Disease," *Proceedings of the National Academy of Sciences* USA 87:1913-1916, 1990; N.W. Barton, R.O. Brady, J.M. Dambrosia, et al., "Dose-Dependent Responses to Microphage-Targeted Glucocerebrosidase in a Child With Gaucher Disease," *Journal of Pediatrics* 120:277-280, 1992; N.W. Barton, G.J. Murray, and R.O. Brady, "Hematological Responses Are Dependent on the Amount of Glucocerebrosidase Administered to Patients With Gaucher's Disease," Blood78:431a, 1991; N.W. Barton, R.O. Brady, J.M. Dambrosia, et al., "Replacement Therapy for Inherited Enzyme Deficiency-Microphage Targeted Glucocerebrosidase for Gaucher's Disease," *New EnglandJournal ofMedicine 324:1* 464-1470, 1991; N. Barton, Chief, Clinical Investigation Section, Developmental and Metabolic Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, personal communication, January 21, 1992; M.D. Grabowski, Department of Genetics and Molecular Biology, Mount Sinai Medical Center, New York, NY, personal communication, January 21, 1992; S. Fallet, M.E. Grace, A. Sibille, et al., "Enzyme Augmentation in Moderate to Life-Threatening Gaucher Disease, *Pediatric Research 31 :496-502, 1992;* A. Taunton-Rigby, Senior Vice President, Bio-Therapeutics, Henri Termeer, Chief Executive Officer, and David McLachlan, Senior Vice President, Chief Financial Officer, Genzyme, personal communications, Boston, MA, February 26, 1992; R.O. Brady, J.M. Dambrosia, and N.W. Barton, "Effectiveness of Low-Dose Replacement Therapy in Gaucher's Disease," Clinical *Research* 40:144A, 1992; G.M. Pastores, A.R. Sibille, and G.A. Grabowski, "Enzyme Augmentation Therapy in Gaucher Disease Type 1: Dosage, Efficacy and Adverse Effects," *Clinical Research 40:357A, 1992.*

sidase; one is present in low concentration but has an enhanced ability to bind the enzyme; the other receptor is present in much greater quantities but is less able to bind the enzyme (21,28,53). Consequently, the Scripps researchers believe that when high doses of the enzyme are administered as suggested by NIH, it quickly saturates the former or high affinity receptors. Most of the enzyme then goes to the low affinity receptors, where it is degraded without alleviating the patient's symptoms. The scientists who favor high-dose therapy do not dispute the existence of a low-affinity receptor; they only take issue with the idea that it plays a role in the absorption of the enzyme. They argue that the high affinity receptors are not saturated with enzyme until doses exceed 100 units/kg (10,13,15). The Scripps investigators favor more frequent therapy because they believe that the intra-cellular half-life of the enzyme is about 8 hours. Giving large amounts of the enzyme every 2 weeks essentially loads the target cells with excessive amount of enzyme which delivers no therapeutic effect after 1 or 2 days. Table 4 summarizes the chief arguments on each side of this controversy.

All patients experienced a decrease in the size of the liver of a similar magnitude to the NIH patients on the high dose unfractionated therapy. In the patients who had not undergone spleen removal, the spleen became smaller. The blood counts increased in all of these patients but the Scripps study does not state whether these changes were statistically significant.

Approximately 10 other patients at Scripps and 10 in Israel are also receiving the lower dose regimen. Their response has been similar to the published results from the Scripps study (20,21). Results have been published on only three of these patients from

Table 4-Scientific Basis for Biweekly High-Dose Unfractionated Versus Low-Dose Fractionated

Dosing regimen	Theoretical basis
80 units/kg for first year of therapy administered every 2 weeks	. Single type of macrophage receptor for glucocerebrosidase which is not saturated at doses below 100 units/kg. . The glycolipid acoumulates slowly in untreated patients, and giving the enzyme more frequently confers no therapeutic advantage.
30 units/kg every 4 weeks, usually spread out over 12 infusions (i.e., 3 times a week)	. Two types of receptors for the enzyme: a low concentration of high affinity receptors and a high concentration of low affinity receptors; high doses rapidly saturate the latter receptors where the enzyme confers little therapeutic benefit; low doses bind preferentially to the former receptors where drug exerts much greater effect. • Intracellular half-life of the enzyme is 8hours; therefore giving large amounts of the enzyme infrequently loads target cells with enzyme which delivers little effect after a few days.

SOURCES: N.W. Barton, G.J. Murray, and R.O. Brady, "Hematological Responses Are Dependent on the Amount of Glucocerebrosidase Administered to Patients With Gaucher's Disease," *Blood* 78:431a, 1991; N. Barton, Chief, Clinical Investigation Section, Developmental and Metabolic Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, personal communication, January 21, 1992; E. Beutler, Chairman, Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA, personal communication, January 21, 1992; M.L. Figueroa, Y. Sate, A. Kay, and E. Beutler, "Efficacy of Frequently Administered Microphage-Targeted Glucocerbrosidase in the Treatment of Gaucher Disease," *Clinical Research* 40:167A, *1992.*

Israel, all children. The two most severely afflicted received 30 units/kg every 4 weeks spread out over 12 infusions (three times weekly), while the least ill received the same 30 units/kg every 4 weeks spread out over only four infusions. The first two patients had more dramatic hematologic and organ responses, suggesting that frequency of infusion may be as important as dose (1,125).

Mount Sinai Medical Center

In a published study conducted at Mount Sinai Medical Center in New York, researchers administered alglucerase for 6 to 12 months to three children and eight adults with moderate to severe Type 1 Gaucher disease; two received 30 units/kg biweekly, three 50 units/kg biweekly, and the remaining six 60 units/kg biweekly (52). Four patients were splenectomized. Within 6 months, the red blood cell count increased in all patients, the platelet count increased in eight patients, and the liver and spleen size decreased in all. The average responses were of similar magnitude to those observed by NIH after 9 to 12 months of therapy. Furthermore, the Mount Sinai investigator concludes that responses were independent of the dose and presence of a spleen.

More recently in a published abstract, the investigator reported his preliminary findings in giving doses of alglucerase of 15 to 60 units/kg biweekly to 34 patients (age 2 to 71 years; 16 splenectomized) with moderate to life-threatening Type 1 Gaucher disease. Red blood cell and platelet counts increased within 3 to 12 months and hepatic and splenic volumes decreased by 12 to 18 months. The change in red cell blood counts and organ (liver and spleen) size were not clearly related to the initial dose (30 to 60 units/kg biweekly) and the rate of organ decrease was not related to dosage decrease, thus tending to reinforce the earlier results. Improvement in blood counts was slowed in those with the largest spleens.

Conclusions Regarding Efficacy

The existing clinical experience suggests the following conclusions about the efflcacy of enzyme replacement therapy:

a) It is generally accepted that alglucerase injections are beneficial for those patients with Type 1 Gaucher disease who have sufficiently low blood counts or enlarged livers and spleens or bone disease to cause symptoms (1,11,20,27,36,52,53,61,65,92,93,95,107,125). No significant toxicity has been observed.
b) Since the enzyme replacement therapy gradually metabolizes accumulated glycolipids, it would be of no use in quickly ameliorating acute crises of severe bone pain or uncontrolled bleeding.
c) Clinical experience with the treatment has been too limited to assess its impact on mortality in the peer reviewed literature. However, according to Genzyme and other researchers, patients who were pre-terminal prior to the initiation of enzyme replacement therapy now enjoy a functional lifestyle (10, 61,107).
d) It is unclear at what stage in the disease a patient should begin therapy. Alglucerase may be most effective if it is given to younger patients, before accumulating glucocerebro-

side deposits have irreversibly damaged normal tissue. Some researchers advocate initiating treatment before the patient becomes symptomatic, believing that it might arrest the development of disease (32,61). As suggested earlier in this paper, such an approach could dramatically increase the number of patients on enzyme replacement therapy. However, at this time, nothing is known about long-term adverse effects of alglucerase. It is possible that the therapy itself will cause adverse effects in patients who would never experience the symptoms of Gaucher disease. In addition, such a treatment strategy might also outstrip the manufacturer's ability to supply the drug.[8]

Conclusions Regarding Appropriate Dosing Regimens

Much of the published literature has concerned initial therapy of Gaucher disease with alglucerase. However, therapy is likely to be given in two phases, an initial phase (presumably with relatively high total doses) to remove accumulated glycolipid deposits from the tissues, and a maintenance phase (lower dose) to prevent the reaccumulation of the deposits. Investigators are currently evaluating the most effective doses and dosing schedule for both phases of therapy.

Initial Therapy

Uncertainty surrounds the choice of an initial dosage strategy. Most experts believe that the initial dose required to metabolize the glycolipid debris in a moderate to severely ill patient with a spleen must be about **60** units/kg biweekly ***(high-dose unfractionated therapy).*** For those patients with less severe disease, an initial dose as low as 10 to 30 units/kg biweekly may be sufficient (10,13). Others suspect that lower doses administered three times a week ***(low-dose fractionated therapy) are*** more efficacious (20,21,28,53). These researchers base this claim on two hypotheses summarized earlier: 1) the enzyme half-life is very short; and 2) there are two types of receptors that absorb glucocerebrosidase.

The proponents of high-dose unfractionated therapy do not believe that a second low affinity receptor for glucocerebrosidase plays an important role. They claim that the rate of accumulation of glucocerebroside in untreated Gaucher patients is slow and that there is no advantage to frequent infusions. The total dose of enzyme, not the frequency of administration, determines the patient's response to therapy. Furthermore, they argue that the high- and low-dose trials that have been conducted are not directly comparable, since some patients participating in the low-dose fractionated studies did not have a spleen. The absence of a spleen, the greatest reservoir for stored glucocerebroside, may have decreased these patients' requirement for the drug, thus increasing its apparent effectiveness. Definite conclusions cannot be drawn about the relative efficacies of these regimens because there has been no direct comparison in one study drawing from the same patient populations. Furthermore, because they enrolled small numbers of patients, the studies do not have the statistical power to detect modest differences in effectiveness.

Maintenance Therapy

There is even greater uncertainty about the appropriate dose for long-term therapy. Genzyme believes that the NIH liver biopsy data and recent NIH dosage reduction studies (10,13), previously described, suggest that after about 12 months of high-dose therapy, a maintenance dose of 7.5 to 15 units/kg biweekly ***(low-dose unfractionated therapy)*** may be adequate to control the patient's problems. However, the NIH investigations are too preliminary to support such a conclusion (21,61). The NIH trials did not even attempt to lower the dose until 2 years of high-dose therapy had been completed, and they have not even begun to treat any patients with a maintenance dose lower than 15 units/kg biweekly.

In Summary, the clinical evidence supports the efficacy of two dosing strategies for moderate to severely ill patients. Because the clinical experience involves small numbers of patients with varying degrees of disease severity, and some with and some without spleens, the relative efficacy of these two regimens has not been established:

- High-dose unfractionated therapy (30 to 60 units/kg biweekly) for one to two years depending on disease severity, followed by maintenance therapy using a low-dose unfractionated regimen (probably 15 to 30 units/kg biweekly). There is as yet no published evidence to support

[8] Potential constraints on the quantity of aglucerase that the manufacturer could produce are discussed in a later section of this paper.

the efficacy of maintenance therapy with a dose lower than 15 units/kg biweekly.

. Low-dose fractionated therapy (2.3 units/kg thrice weekly). Researchers investigating this regimen believe that if the high-dose unfractionated therapy can be reduced after about 1 year, then this low-dose fractionated strategy can also probably be reduced.[9] The minimum effective dose for such a strategy has not been established (21).

THE DISCOVERY AND DEVELOPMENT OF ALGLUCERASE

To bring a new drug to market, a company must invest in the research and preclinical and clinical development required for approval by national agencies in charge of new drug approval (47). In the United States, the FDA is the national agency whose requirements for new drug approval govern entry to the market. Even after a company files a New Drug Application (NDA)-a request to market the drug in the United States—it may conduct additional R&D on new formulations, drug dosage forms, manufacturing processes, or indications for use. Genzyme is no exception. The company incurred substantial costs in developing its placental form of alglucerase for the market.

In the case of alglucerase, however, direct and indirect Federal subsidies for R&D had a major impact on the costs of attaining market approval for the drug. NIH bore a substantial part of the costs of R&D. The FDA expedited the review of the drug and granted Genzyme limited rights to sell the drug before it was approved for marketing under a provision known as the "Treatment IND."

This section outlines the history of the alglucerase R&D process and presents estimates of the total cost of obtaining market approval for Genzyme's placental form of alglucerase (marketed under the brand name Ceredase™), including estimates of the portion of the cost borne by three groups: the private investors in Ceredase™, NIH, and the consumers who paid for the drug before it was approved for marketing. Table 5 contains a brief of the critical milestones in the development process.

Table 5-The Development of Ceredase

Date	Milestone
1965	Gaucher disease first attributed to glucocerebrosidase deficiency.
1974	Enzyme replacement therapy first attempted at NIH as a treatment for the disease.
1981	Genzyme begins to supply NIH with the enzyme
December 1983	First successful treatment with the modified form of the enzyme is begun at NIH.
March 1985	Genzyme receives orphan designation for the modified placenta-derived enzyme.
September 1987	Clinical Partnership (Genzyme Clinical Partners, L. P.) established with $10 million to fund research and development.
March 1988	FDA allows Genzyme's IND application for Ceredase, its trademarked name for the modified enzyme.
March 1989	Clinical trials begin at NIH with 12 Gaucher's patients.
October 1989	Treatment IND protocol approved by FDA.
February 1990	Clinical partnership bought out by Genzyme.
April 1990	Genzyme files an NDA for Ceredase.
April 1991	FDA approves Ceredase for the treatment of Gaucher disease (Type 1).
November 1991	Genzyme receives orphan designation for a recombinant form of the enzyme.

KEY: FDA - Food and Drug Administration; IND - Investigational New Drug; NDA - New Drug Application.

SOURCE: Office of Technology Assessment, 1992.

History of Alglucerase Development

Genzyme Corporation: Background

Founded in 1981, Genzyme is a diversified pharmaceutical company with four divisions: biotherapeutics, diagnostic products, diagnostic services, and pharmaceuticals and fine chemicals. The company's general strategy, according to its 1991 annual report, is to take advantage of its expertise in carbohydrate engineering, protein chemistry, and enzymology to develop and sell profitable health care products. The strategy appears to have been successful: the price of Genzyme's stock rose from less than $13.50 per share in the second quarter of 1986, when the company went public, to $42.00 as of September 1, 1992. The stock has traded at prices as high as $66.50. In 1990, the year prior to FDA approval of alglucerase, the company reported total revenue of approximately $55 million, derived mainly from product sales and revenue from R&D contracts. The company had 1991 revenues of approximately $100 million. Alglucerase sales accounted for approximately $37.25 million of this total (73,86,107).

[9] These researchers have not presented evidence to support this suggestion.

The company manufactures its products at four sites in the United States and England, and it employs approximately 850 people worldwide (650 in the United States). About 40 percent of the employees are involved in manufacturing and distribution, 25 percent in R&D, and about 18 percent in marketing and sales. The remaining 17 percent work in administration or finance.

Ceredase™, the Biotherapeutics group's flagship product, is expected to have sales of $200 million by 1993 (4). At least 12 other products are in various stages of development, regulatory review, and production. The company is also aggressively pursuing the development of the recombinant DNA (genetically engineered) form of the enzyme (currently in clinical trials) and is building a new facility to manufacture it in larger quantities[10]; clinical trials using the recombinant form are expected to be completed by the end of 1992 (107).

Orphan Designation for Alglucerase

The Orphan Drug Act, enacted in 1983, provides potentially sizable financial incentives for the development of treatments for rare disorders (i.e., those affecting 200,000 or fewer people in the United States). When a drug under development is given orphan status by the FDA, it is eligible for a 50 percent income tax credit on qualifying clinical research.[11] At the time it was developing the placental form of alglucerase, however, Genzyme had no current tax liability, so it could not use the tax credit. The most powerful incentive in the law for a company such as Genzyme is that the FDA grants a 7 year period of exclusive marketing to the frost firm whose orphan product obtains FDA approval for a specific indication. Because NIH had discovered alglucerase, Genzyme could not rely on patent protection to ensure an adequate return on its investment. As a result, without orphan designation, Genzyme would have had to rely solely upon proprietary information to give it a competitive edge. Given the difficulty in maintaining the secrecy of the manufacturing process, such an advantage would have been a shaky foundation on which to begin the development of a new drug. Thus, orphan drug designation was an important stimulus to the development of this drug.

Genzyme filed for orphan designation for alglucerase in 1983 and officially received orphan status from the FDA in March 1985.

R&D Limited Partnership for the Development of Alglucerase

After the FDA granted orphan status for alglucerase, Genzyme entered into a joint venture with a limited partnership, Genzyme Clinical Partners, "to develop, manufacture and sell injectable products incorporating modified forms of the enzyme. . ." (59). Genzyme Development Corporation, a wholly-owned subsidiary of Genzyme, was designated the general partner of the venture (the general partner is the party with unlimited financial liability). Beginning in September 1987, the joint venture made Genzyme responsible for conducting human clinical trials, improving the manufacturing process, and seeking FDA approval for alglucerase (59). The limited partners contributed $10 million to this endeavor. In return for undertaking this research, the corporation was reimbursed by the partnership for its quarterly projected costs, plus a 7 percent fee. The agreement also stipulated that Genzyme would contribute additional research funds, if necessary, to further develop and market the product (107). The partnership received an immediate $400,000 cash payment and a 2 percent royalty on future product sales for the use of some proprietary technologies.

Under the terms of the joint venture agreement, any future product would be marketed through Genzyme, at a cost to the joint venture of 28 percent of selling prices net of certain expenses. Fifty percent of the profits from any product sales were to go to Genzyme and 50 percent to the partnership. After 36 months, Genzyme had an option to acquire all rights to the developed technology for $10 million in cash and stock and a 4 percent royalty on product sales to the year 2000. As part of the initial partnership agreement, Genzyme granted warrants to the investors in the partnership. These warrants entitled the investors to the right to purchase just over 300,000 shares of common stock at prices ranging from $18.125 per share to $20.125 per share from September 1, 1989 through August 31, 1994.

After the Partnership's initial funding ran out at the end of 1989, Genzyme bought out the partner-

10 This facility will also house other Genzyme operations.

11 "Qualifying research" is defined by the Internal Revenue Service as excluding all management and supervision expenses except the direct supervision of scientists and technicians. Thus, not all clinical research expenditures are eligible for the tax credit.

ship in February 1990. From this transaction, the partners received 1,406,000 shares of common stock valued at approximately $21 million (59). Genzyme charged this expense to "purchase of in-process research and development" in its statement of operations.

The Regulatory Process

Genzyme received approval for an IND application to begin clinical trials of its modified form of the enzyme in March 1988 (102). Primarily on the basis of encouraging results from the l-year NIH study involving 12 patients (11,89), Genzyme fried its NDA for alglucerase in April 1990 and received approval 1 year later. Although the FDA usually requires randomized clinical trials to establish efficacy, such studies are often impractical for rare conditions. In approving alglucerase, the FDA relied almost exclusively on observational studies. The approval of the NDA was expedited by Subpart E designation, a new FDA regulation designed to expedite the review of drugs for life-threatening or severely debilitating illnesses (115). (This regulation is separate from the provisions of the ODA.) Genzyme chose not to receive official protocol assistance from the Office of Orphan Product Development, relying instead on informal channels of communication (107).

Treatment IND

Between October 1989 and April 1991, alglucerase was made available to patients around the country under the FDA's Treatment IND program. This program is designed to facilitate access to experimental drugs for the treatment of otherwise untreatable diseases. Under this arrangement, Genzyme sold the drug to patients not enrolled in clinical trials whose physicians agreed to abide by a specific protocol (107,1 15). As part of Treatment IND regulations, Genzyme was entitled to charge patients a price sufficient to recover the "costs of manufacture, research, development, and handling of the investigational drug (115). " The FDA approved a price of $3.00 per unit. After final FDA approval signified the end of the Treatment IND program, the market price of alglucerase was set at $3.50 per unit (107).

Genzyme and NIH

By the end of 1975, NIH researchers had patented their method for harvesting the enzyme. Between 1976 and 1981, NIH contracted with the New England Enzyme Center at the Tufts University Medical School to supply it with sufficient quantities of the enzyme in accordance with the NIH-devised protocol (107). During this period, the contracts amounted to almost $1 million. The terms and amounts of these contracts are summarized in table 6.

Table 6-NIH Contracts Pertaining to Alglucerase

Year	Purpose of contract	Principal investigator	Amount
1976	Harvest glumcerebrosidase from human placentae using a previously published procedure, with a slight modification in the ammonium sulfate fractionation step.	Henry Blair, Tufts University	$ 50,000
1977	Harvest glucocerebrosidase in increased quantities.	Henry Blair, Tufts University	185,000
1978	Harvest glucocerebrosidase in increased quantities.	Henry Blair, Tufts University	403,373
1980	Harvest glucocerebrosidase in increased quantities.	Henry Blair, Tufts University	20,000
1981	Harvest gluoocerebrosidase in increased quantities.	Henry Blair, Tufts University	292,500
1982	Harvest glucocerebrosidase from placental tissue.	Henry Blair, Genzyme	355,770
1983	Harvest glucocerebrosidase from placental tissue.	Henry Blair, Genzyme	545,454
1984	Harvest glucocerebrosidase from placental tissue.	Henry Blair, Genzyme	405,985
1985	Harvest glucocerebrosidase from placental tissue.	Henry Blair, Genzyme	295,383
1987	1. Harvest enzyme at high purity for clinical trials. 2. Develop enzyme targeting strategies. 3. Develop methods to enhance current 8-hour half-life. 4. Develop techniques to enhance enzyme delivery to target cells. 5. Produce antibodies to human glucocerebrosidase for use as diagnostic probes and to facilitate isolation of the human gene.	Henry Blair, Genzyme	54,964
1988	Same as 1987.	Henry Blair, Genzyme	414,006
1989	Harvest glucooerebrosidase from placental tissue.	Scott Furbish, Genzyme	551,174
1990	Harvest glucocerebrosidase from placental tissue.	Scott Furbish, Genzyme	1,992,060
1991	Harvest glucocerebrosidase from placental tissue.	Scott Furbish, Genzyme	2,000,000
1992	Harvest glucocerebrosidase from placental tissue.	Genzyme	2,300,000
		Total	$9,865,669

SOURCE: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, 1992.

In 1981, the center closed down, and Genzyme, then a fledgling pharmaceutical company, took over the contract to supply the enzyme. The transition was easily achieved since Henry Blair, the former head of the center, was also one of the founders of Genzyme. In the following 11 years, the NIH contracts with Genzyme totaled nearly $9 million. Under the terms of these agreements, Genzyme supplied enzyme for the clinical trials conducted at NIH. Between 1983 and 1988, Genzyme furnished enzyme for two previously described studies, one involving a single patient and a second enrolling 23 subjects. Between 1989 and 1991, Genzyme supplied the enzyme for a high-dose trial involving 12 participants. For a total of 8 months during this interval, Genzyme supplied the enzyme free of charge. Currently, the company is providing modified glucocerebrosidase for a low-dose study and a protocol involving Type 3 patients as part of its current contract with NIH (see table 6).

Because NIH and others had published papers discussing harvesting, purification, and modification strategies, these processes were not patentable. However, Genzyme claims that its current procedure for harvesting the enzyme from human placental tissue and modifying it bears little resemblance to the original NIH-devised protocol, and that it has now sufficiently changed the original NIH process to obtain patent approval (107). It claims the original process had a much lower yield per unit of tissue, with a higher degree of impurity (107). Because Genzyme's protocol is proprietary, we are unable to determine the extent to which it differs from previously published protocols and the 1975 patent. This patent will expire in October 1992.

The Cost of Developing Alglucerase

To bring a new drug to market, investments are required in both R&D and manufacturing facilities and equipment. Most studies of the costs of pharmaceutical R&D do not include the costs of manufacturing design, engineering, or construction in estimates of R&D costs (e.g., 47,68). In the case of Ceredase™, a large fraction of the costs associated with bringing the drug to market were (and continue to be) for improving the manufacturing process and assuring quality control, and Genzyme charged these costs to R&D accounts (107). To the extent that they can be separately identified, the costs of investing in manufacturing capacity are excluded from estimates described in this section but are discussed in a later section on the cost of producing, marketing, and distributing the drug.

Three different sets of "investors" bore the costs of discovering and developing the placental form of alglucerase: NIH, the investors in Genzyme's Ceredase™ enterprise (including both the investors in the R&D Limited Partnership and the owners of Genzyme Corporation), and the consumers or their health insurers who purchased Ceredase™ under the treatment IND.

NIH Investments in Alglucerase

Most of the early costs of **identifying,** synthesizing, and testing alglucerase were borne directly by NIH, as either intramural or extramural (contractor grant) research. Table 6 shows that between 1976 and 1981, a total of $950,873 was spent under NIH contracts for research pertaining to alglucerase. These expenditures do not count intramural research (work funded by NIH on its own campus) expenditures or any extramural grants to researchers other than Genzyme or the New England Enzyme Center. NIH accounting systems do not allow estimation of the intramural spending on Gaucher disease.

The NIH contribution did not end when the drug entered the clinical testing phase. Some of NIH's clinical expenditures were intramural and cannot be estimated directly. For example, NIH researchers conducted the pivotal clinical trial for FDA approval. NIH contracted with Genzyme to provide quantities of alglucerase sufficient to conduct its clinical research. Between 1982 and 1992, NIH spent $8.9 million on contracts with Genzyme for this purpose. The total contribution of NIH, excluding the costs of intramural research, was $9.7 million.

Consumer Investments in Experimental Alglucerase

The company sold approximately $6 million of alglucerase between October 1989 and April 1991 under the treatment IND program (102), but the company has, in total, written off or still has outstanding receivables totaling about 10 percent of the IND revenues (73,86,107).

Private Investments in Alglucerase

On the basis of information supplied by the Genzyme Corporation (107a), we estimate that Genzyme spent approximately $29.4 million on R&D for placental alglucerase on behalf of its

investors and its contracts with the R&D Limited Partnership. These expenditures spanned the decade preceding the product's introduction to the market in 1991. They represent only the cash outlays, not the fully capitalized cost of bringing Ceredase to market. Genzyme claims that much more was spent in cash outlays for R&D, about $48.6 million, but it includes in that amount the difference between the cost of the 1990 buyout of the R&D Limited Partnership ($20.8 million) and the partnership's initial investment of $10 million as well as the net gain to the holders of the Partnership's warrants on the exercise date ($8.4 million). These payments do not represent actual expenditures for the work, materials, and facilities needed for the conduct of R&D. They are part of the purchase price of the valuable asset that Ceredase[tm] had become by the time the partnership was bought out by the company.[12])

With the data available to us, it is impossible to estimate the time profile of private spending on R&D. About 14 percent ($4.2 million) of Genzyme's expenditures for R&D were spent before 1987, the year in which the R&D Limited Partnership was formed. According to Genzyme's 1991 annual report, the $10 million raised from the Partnership was fully spent by the end of 1989. A large part of Genzyme's R&D expenditures include part of the cost of purchasing Integrated Genetics, Inc. in 1989, whose assets were used in part to further develop and manufacture placental alglucerase (73).

Genzyme's development of treatments for Gaucher disease are not over. Research and development are currently underway for a recombinant form of glucocerebrosidase that would potentially be both safer and cheaper to produce. We did not analyze the financing costs of the research leading to this potential new product.

Conclusions About the Discovery and Development of Alglucerase

The cost of developing alglucerase for FDA approval was borne by three parties-the Federal Government NIH), private investors in the Ceredase enterprise, and consumers or their insurers who paid for the drug while it was still experimental. The relative contributions of these three parties cannot be estimated, because NIH's intramural costs have gone uncounted. Of the costs that were counted, NIH paid for at least 20 percent.

THE COST OF MANUFACTURING, DISTRIBUTING, AND MARKETING PLACENTAL ALGLUCERASE

Since it was approved for marketing in April 1991, the price of Genzyme's alglucerase has been $3.50 per unit. The cost of producing alglucerase may be higher than that of many other drugs because of the complicated process of harvesting placentae and extracting and purifying the enzyme from placental tissue. Genzyme Corporation provided us with estimates of the cost of producing placental alglucerase in 1991 and 1992(107). The cost per unit before taxes was estimated at $2.34 in 1991 and $1.90 in 1992.[13] The unit costs decreased in part because the volume of production increased dramatically between 1991 and what is estimated for 1992. Based on revenue data and the price of the drug, production rose from approximately 11 million units in 1991 to at least 27 million units in 1992. As a result, fried costs are allocated across larger production and distribution volumes. If the volume of product increases over time, the unit cost can be expected to decrease further, although probably at a decreasing rate. Genzyme contends that its current production arrangements with the placenta-harvesting organization limit its total production of the placental form of alglucerase to 40 million units.

The per-unit costs also include a relatively high percent of sales expected to be bad debts and free goods. In 1992 bad debts and free goods together are projected to constitute 14 percent of revenues. Although few accounts have to date been written off as uncollectable (86), Genzyme does not expect to collect the full amount of the purchase price from all patients or their insurers.

The per-unit cost estimates provided by Genzyme include charges for depreciation on facilities and

[12] **Conservative accounting procedures demand that payments for rights to market drugs not yet approved by the FDA be accounted for as the purchase of in-process R&D and not shown as assets. Once a drug is approved by FDA, the purchase is recorded as a purchase of product technology and may be amortized over its expected life.**

[13] **Genzyme claims its unit costs are higher than the numbers presented here, but the company allocated the Cost Of ongoing R&D expenditures (not related to placental alglucerase) to the cost of the product.**

equipment used in manufacturing, distributing, and selling placental alglucerase. Genzyme invested in freed manufacturing capacity early, before the product was marketed, and continues to incur freed manufacturing expenses. Genzyme estimates that its expenditures for freed manufacturing assets between 1981 and 1994 will total over $11 million (107a). Depreciation charges probably do not reflect the true economic cost of such facilities, however, because they are only a very rough and imperfect approximation of the actual loss of market value of the assets in each year. It is impossible with the information at hand to determine the extent to which depreciation expenses included in the unit cost estimates understate or overstate the true costs of manufacturing and marketing alglucerase.

Genzyme's estimates of unit costs imply that each unit sold will contribute about $1.60 in 1992, and somewhat more in future years, to repaying the investors in placental alglucerase R&D. This estimate does not take the effect of taxes into account. Analyzing the after-tax contribution of alglucerase revenues to repayment of the investors in alglucerase R&D is complicated. Taxes must be paid on the taxable income from sales of alglucerase, but tax deductions and credits were also earned on the R&D that Genzyme undertook either on its own or on behalf of the alglucerase R&D Limited Partnership. Such tax deductions and credits effectively reduced the net cost of R&D. Although Genzyme had net tax losses in its early years, a large proportion of these losses could be carried forward and charged against its net income in future years. Because of the disparities in amount and timing of tax liabilities, deductions, and credits, it is impossible to estimate the after-tax contribution of alglucerase revenues to the repayment of the after-tax private investment in alglucerase R&D.

We do not report the internal rate of return[14] to the private investments in alglucerase because it is impossible to determine the true contribution of alglucerase revenues to repaying the R&D investment. Placental aglucerase is only one of many projects that the company was involved in, and many arbitrary decisions are required to allocate costs to any single project. Although we did not attempt to assess the project's rate of return, for many successful R&D projects the returns must be high to compensate for the risks of failure. In the case of alglucerase, however, the risk was probably not commensurate with the risk associated with the development of most other pharmaceuticals. Much of the basic research was performed by NIH, and the probability of success by the time the Limited Partnership was formed must have been quite high.

POTENTIAL ADVANCES IN THERAPY FOR GAUCHER DISEASE

Currently, NIH is exploring ways to increase the amount of infused enzyme absorbed by the macrophage cells (10). NIH is also planning to examine the effects of alglucerase on the nervous system in patients with Type 3 Gaucher disease, particularly those who are unable to voluntarily move their eyes from side to side (10). This latter research could lead to an expansion in the market for alglucerase.

A recombinant form of glucocerebrosidase has recently been developed by putting the genetic information necessary to create the enzyme into a non-human cell, usually from an animal (103). Both Genzyme and an NIH researcher have applied for patents covering this process. Although no patent has been issued yet, NIH has awarded licenses for the use of its process to both Genzyme and Enzon Inc., a pharmaceutical company in Plainfield, New Jersey. Genzyme is currently producing a recombinant form of the enzyme. Enzon has not indicated when its form might be ready for clinical trials (101). NIH and Mount Sinai Medical Center initiated trials with recombinant therapy early in 1992 (10,61). This recombinant form of the drug is potentially safer because it poses less risk of viral contamination than when the enzyme is harvested from the biological materials of several million different people, such as from their placentae.

It is possible that in the future genetically modified animals may be utilized to produce human proteins such as glucocerebrosidase in their milk. For example, scientists have developed transgenic goats whose milk produces a variant of human tissue plasminogen activator, a substance used to destroy

14 The internal rate of return is defined as the rate of interest at which the present value of expected cash inflows is equal to the present value of expected cash outflows. Put another way, it is the interest rate at which a company could borrow money to fund the project and still break even.

the blood clots obstructing the coronary arteries during a heart attack (49).

Other researchers hope that gene transfer will be a means for treating Gaucher disease. In this technique, scientists would develop a means to introduce the normal glucocerebrosidase gene into the tissues of a Gaucher patient in the hope the gene will be incorporated into the patient's DNA and reproduced indefinitely (72,77). One of the most promising such strategies would use a type of virus known as a retrovirus. Scientists would remove the parts of the virus's genetic material necessary for reproducing itself and replace it with a normal glucocerebrosidase gene. Physicians would mix the virus with bone marrow cells that have been removed from the patient and then reinfuse them into the patient. Prior to reintroducing the genetically modified bone marrow cells, physicians must obliterate the patient's own bone marrow because cells carrying the abnormal glucowrebrosidase gene would otherwise survive and continue reproducing. Because elimination of the bone marrow leaves the patient susceptible to infection, anemia, and uncontrolled bleeding during the recuperation period, this procedure would be risky (7,20).

Further compounding the problems associated with gene transfer is the difficulty of infecting very immature forms of human blood cells. Although researchers have been able to correct the enzyme deficiency in a small number of patients by infecting more mature blood cells with the normal glucocerebrosidase gene (54,103), they have not yet succeeded in incorporating the gene into immature cells with the capacity to reproduce themselves. Therefore, any normalization of the enzyme activity achieved by gene transfer will only be temporary, and the procedure (called transection) will need to be repeated periodically.

Other therapies under consideration include: techniques to enhance the efficiency of the enzyme by synthesizing a compound to enhance its activity; methods to inhibit the body's ability to synthesize glucocerebroside; and methods to inhibit the release of toxic substances from the macrophages already engorged with glucocerebroside (7). These toxic substances are believed to cause some Gaucher symptoms.

PAYING FOR ALGLUCERASE THERAPY

This section examines the cost of alglucerase therapy, the current system of paying for it, and the implications of this system for patients, their families, and their insurers.

Cost of Treatment

The cost of alglucerase therapy depends on the particular regimen used, varying with dosage (measured in units per kg), dosing interval (number of doses per year), weight of the patient (in kg), and price per unit of alglucerase. To understand better the cost and financing of alglucerase, we examine the four treatment regimens that were reviewed above. The estimates that follow are not meant to imply that all patients follow one of these exact regimens. However, these dosing schedules do yield the range of costs associated with enzyme replacement therapy for Gaucher disease. All regimens are consistent with the FDA-approved labeling for alglucerase (which is discussed in greater detail below):

(a) High-dose unfractionated-60 units/kg each week (1 1);

(b) High-dose unfractionated followed by maintenance therapy-6O units/kg biweekly for 1 year, 30 units/kg biweekly thereafter (10,11);

(c) High-dose unfractionated initial dose followed by lower dose maintenance therapy-30 units/kg biweekly for 1 year, 15 units/kg biweekly thereafter (10,52,61,95);

(d) Low-dose fractionated therapy-30 units/kg monthly administered three times weekly (as used in Scripps Clinic and in Israel). This regime is equivalent to a dose of 2.3 units/kg per infusion (1,20, 27,53).

Table 7 shows the cost of treating each patient for the first year of therapy, by component of therapy and by regimen type, for a 50-kg individual at the current price of $3.50 per unit. Under the initial dosing protocol for a moderate to severely affected patient (regimen b), the annual cost of alglucerase for a 70-kg individual is $382,200. This price does not include the costs of administering the biweekly injections, nor the cost of associated diagnostic evaluations. The costs of ancillary services like outpatient infusion of the drug and laboratory tests

Table 7—Estimated Annual Per Patient Drug and Ancillary Charges for Alglucerase Therapy Under Four Potential Dosing Regimens

	Dosing regimen			
First year (units)	60	60	30	2.3
Subsequent year (units)	60	30	15	2.3
Frequency(annual)	52	26	26	144
First year drug cost ($/year)[a]	$546,000	$273,000	$136,500	$57,960
Subsequent year drug cost ($/year)[a]	$546,000	$136,500	$68,250	$57,960
Anciilary charges[b]				
Infusion	3,640	1,820	1,820	10,080
Complete blood count	720	720	720	720
Liver function tests	1,200	1,200	1,200	1,200
Magnetic resonance imaging	1,200	1,200	1,200	1,200
Total ancillary charges	$6,760	$4,940	$4,940	$13,200
Total first year cost of therapy (annual)	$552,760	$277,940	$141,440	$71,160
Total subsequent year cost of therapy (annual)	$552,760	$141,440	$73,190	$71,160

aThese figures assume a unit price of $3.50, the cost of alglucerase for privately insured patients.Thereare discounts available to Medicaid recipients and those who exhausted their insurance benefits, as discussed in the text. Costs are computed using an average patient weightof 50 kg, a figure which was computed from a distribution of patient weights provided by Genzyme.
b The charge for each infusion is $70.All regimens include a complete blood count twice a month($30 each),a liver function test twice a month($50each), and magnetic resonance imaging twice a year($600 each). Charge data are average allowed charges from Blue Shield of California.

SOURCE: Office of Technology Assessment, 1992.

range from $4,940 to $13,200 annually, depending on the treatment regime (87).[15]

The cost of treatment can be greatly reduced by lowering the dosage. Genzyme advocates a maintenance dosing therapy of as little as 7.5 units/kg administered biweekly. An NIH researcher is using 10 units/kg biweekly as initial therapy in patients who are not severely ill (10). For these regimens, the annual cost of therapy for an average patient would be between $34,125 and $45,500 (without ancillary costs). However, as noted earlier, there are no published reports of responses to therapy among moderately to severely ill patients treated with maintenance doses of less than 15 units/kg biweekly. Furthermore, although the per-patient costs of the 10 units/kg biweekly regimen are relatively low, this regimen would be unlikely to reduce aggregate expenditures on alglucerase. It would add the expenditures for treating the large population of patients with less severe forms of Gaucher disease to the expenditures for treating more severely ill patients with a higher dose regimen. Thus, one could view this regimen as an approach to expanding treatment to a broader population, not as an approach to reducing costs of treating severely ill patients.

Who Pays the Cost of Alglucerase Treatment?

Table 8 shows the distribution of the first 301 patients to receive alglucerase injection therapy according to the type of health insurance that paid all or part of their alglucerase expenses on December 31, 1991 and a similar distribution for all patients receiving alglucerase on March 31, 1992 (3). Most patients (60 percent) have indemnity insurance either through commercial insurers (25 percent), Blue Cross and Blue Shield (BCBS) plans (21 percent), self-insured employer groups (9 percent), or plans available to Federal employees (4 percent). Fourteen percent receive their medical care through a health maintenance organization (HMO). Almost 13 percent have Medicare coverage either because their medical condition has rendered them disabled or because they are older than 65 years of age. Eight percent have Medicaid coverage, and the remaining 6 percent either have some other type of insurance or none at all. This last group includes patients who receive alglucerase free of charge through the Genzyme Access Program because they lack health insurance.

This picture of coverage may not be representative of the insurance status of all Gaucher patients who will ultimately receive alglucerase therapy. The

15 These costs remain the same for patients in dosing regimens b and c regardless of whether they are receiving initial treatment or a lower maintenance dose since both doses involve the same number of infusions.

Table 8-Distribution of Alglucerase Patients by Primary Payer

Type of payer	Percent of patients as of December 31, 1991	Percent of patients as of March 31, 1992
Medicare	12.8%	12.5%
Medicaid	8.0	8.9
Private health insurance		
Blue Cross and Blue Shield	21.1	20.9
Commercial insurers	25.9	24.3
Health maintenance organizations. .	13.6	13.2
Self-insured groups	8.8	8.7
Federal employee insurers	3.7	4.1
Other including Genzyme's free drug program	5.9	7.5
Total	100.0	100.0
Number of patients	301	NA[a]

[a]Genzyme did not provide data on number of patients receiving alglucerase as of March 31, 1992.

SOURCE: Genzyme, 1992.

patients treated first may differ clinically or in other essential respects from the entire Gaucher population. For example, given the relative expense of the therapy, those patients with the most complete coverage may begin therapy earlier than those who are less well-covered. Furthermore, because insurance status can change over time, the distribution of insurance coverage among these 301 patients could be very different 2 or 3 years in the future. However, these are the only data available that describe insurance coverage of recipients of alglucerase injections.

Insurance Payment for Alglucerase Therapy

For those Gaucher patients with health insurance, payment for alglucerase therapy depends on several factors. These include the status of alglucerase as a covered benefit, the split between the insurer's and patient's responsibilities in paying for covered benefits, the patient's lifetime insurance benefit, and other logistical and administrative issues. To compile this information, we contacted Genzyme, private insurance plans, representatives of Federal health insurance programs, and insurance trade associations.

Coverage

Patients usually receive coverage for alglucerase through the general outpatient medical benefit provisions of their insurance. These benefits cover medically-necessary, FDA-approved drugs administered under a physician's supervision in a medical office or clinic. As described above, alglucerase is usually administered by infusion in a physician's office.[16] Most insurance plans define "medically necessary" to include therapies administered for indications described on the drug's package insert.

Although we found that most private (commercial, BCBS, and HMO) insurers accept a physician's prescription as sufficient evidence of medical necessity, several insurers, especially BCBS plans, subject alglucerase claims to greater scrutiny. Representatives of these plans cited the drug's high price and ambiguity in the labeling of FDA-approved indications and dosing regimens as reasons for their close consideration of claims (5,30,41,46,69,82). The label indicates that alglucerase is indicated for Type 1 Gaucher with: "a) moderate-to-severe anemia; b) thrombocytopenia with bleeding tendency; c) bone disease; [or] d) significant hepatomegaly or splenomegaly." However, the label does not provide any more detailed clinical guidelines to interpret these indications. The dosing regimen, based on the clinical evidence discussed earlier in this paper, also lacks specificity:

> Dosage should be individualized for each patient. An initial dosage of up to 60 unit/kg of body weight per infusion may be used. The usual frequency of infusion is once every two weeks, but disease severity and patient convenience may dictate administration as often as once every other day or as infrequently as once every four weeks. After patient response is well established, dosage maybe adjusted downward for maintenance therapy. Dosage can be

115 A handful of patients have the drug infused in their homes, although insurance coverage of this form of administration tends to be less common than for infusion in the physician's office. Genzyme anticipates that home infusion of alglucerase will increase over time (3). Another recent OTAreport examines *Home Drug Infusion Therapy Under Medicare in* greater detail (114).

progressively lowered at intervals of 3-6 months while closely monitoring response parameters. Ultrastructural evidence suggests that glucocerebroside lipid storage may respond to doses as low as 1 unit/kg.

As described earlier in this paper, the potential dosing regimens for alglucerase consistent with this label imply a wide range of expenses for patients and their insurers.

Private Health Insurers—The most intensive scrutiny of alglucerase claims appears to occur among BCBS plans. Several plans, including those in New York and Massachusetts, require an assessment of patient progress every 6 months in consultation with the patient's physician to determine whether doses might be reduced without compromising the efficacy of the therapy (30,82). The New York plan has also adopted specific clinical guidelines for interpreting anemia, thrombocytopenia, and the other indications for therapy .17 Blue Shield of California recently took the more restrictive step of limiting coverage to the dosing regimen tested at the Scripps Clinic (regimen c in table 7) (5). Based on a review of scientific literature and a meeting of its medical advisory committee, the plan concluded that there is insufficient evidence that more costly regimens are any more effective (i.e., medically necessary) than the Scripps dosing. One plan, BCBS of Connecticut, reported that it is not currently paying any claims until the insurer's medical review committee has studied the drug more carefully (46).[18] Among the commercial plans contacted by the authors, only Aetna has developed its own guidelines for determining the medically necessary indications for alglucerase. Under plans requiring precertification of prescription drugs, such as Aetna's HMOs, these guidelines call for an assessment of patient progress every 3 months (69). The reviews of claims and related patient data required by these plans are more intensive than that performed for most other drug therapies or physician services, undoubtedly as a consequence of the relative infrequency of alglucerase claims, the drug's high costs, and the wide range of potential dosing therapies.

Medicare and the Civilian Health and Medical Program of the Uniformed Services (CHAMPUS)— Medicare covers injectable drugs approved by the FDA when they are provided as part of a physician's professional services for indications specified on the label. For indications other than those on the label, the Health Care Financing Administration (HCFA) allows its "carriers" (private insurance firms and BCBS plans that pay claims for Medicare outpatient services under contract from HCFA) to make coverage decisions. Hence, there can be differences among carriers regarding the coverage of *unlabeled* uses of drugs like alglucerase (31). Although HCFA can issue national coverage guidelines that supersede carriers' decisions, it has not done so for alglucerase, citing the relatively small number of Medicare beneficiaries receiving alglucerase[19] and a query of carriers which indicated that all currently cover alglucerase claims (123).[20] CHAMPUS, the Federal health insurance program run by the U.S. Department of Defense for dependents of uniformed U.S. Defense Department personnel, has not yet received any claims for alglucerase therapy. Since CHAMPUS tries to coordinate its coverage policies with those of HCFA, this program expects to pay for alglucerase therapy needed by its beneficiaries (6).

Medicaid—With the exception of certain federally mandated benefits, States can opt to exclude services from coverage even if a physician considers them to be medically necessary (112). However, those States with Medicaid prescription drug benefits (all States except one) must cover every drug for 6 months following FDA approval (55). According to HCFA, all States that have received claims for alglucerase therapy have continued to pay beyond the 6-month anniversary of approval in October 1991 (70).

17 Genzyme has suggested that these interpretation are overly restrictive because they indicate disease more Severe than that found among some of the patients followed in NH's clinical studies of alglucerase (107a).

18 As of March 1992, BCBS of connecticut had received alglucerase claims for two patients --one who actually held insurance from BCBS and another who held insurance through a self-insuring employer that had contracted with BCBS to administer its claims (3).

19 HCFA expects that there would never be more than 1,000 to 2,000 Medicare beneficiares on alglucerase therapy at any one time. HCFA also believes that because the therapy will enable Gaucher's patients to work in the long run, most Medicare beneficiaries receiving alglucerase will be over 65 years old rather than disabled (31).

20 HCFA usually only makes national coverage decisions when controversy arises among carriers over particular services or therapies (114).

Cost Sharing Between Patients and Insurers for Alglucerase Therapy

Even patients with insurance that covers alglucerase may have to pay out-of-pocket for some of the expenses associated with their therapy. Medicare requires patients to pay 20 percent of the approved fees for physician office visits, including the infusion of drugs and diagnostic laboratory tests. However, about 71 percent of all Medicare enrollees have supplemental health insurance (sometimes called "medigap" policies) that covers all or part of this copayment (43,9 1); Genzyme indicates that a greater fraction, 90 percent, of Medicare beneficiaries receiving alglucerase in March 1992 had supplemental insurance. The benefits that such plans offer vary greatly, so there is little basis for estimating the out-of-pocket expenses of covered individuals. It is clear that the out-of-pocket for Medicare patients who lack supplemental coverage is substantial. Based on the cost estimates in table 7, the expenses could total more than $50,000 per year for a 50-kg Medicare patient who paid the full copayment. In addition, some providers bill patients for more than "allowed" charges and seek payment directly from patients for the difference between the billed and allowed amounts. To the extent that providers "balance bill" for ancillary services,[21] patients' out-of-pocket expenses could even exceed the 20 percent copayments described here.

Most private indemnity insurance plans carry an annual deductible and a copayment (123). Hence, privately insured Gaucher patients also face some out-of-pocket expenses for their alglucerase therapy. However, most private policies place limits on the patient's total annual financial liability for covered services. According to recent national estimates presented in table 9, 83 percent of all beneficiaries of such plans have a limit on out-of-pocket expenses each year (not including premiums) after which the insurer pays 100 percent of covered medical services (123). Almost three-quarters of indemnity beneficiaries have maximum out-of-pocket expenses of $2,100 or less. Genzyme has indicated that as of March 1992, 80 percent of its privately insured customers had a limit of $2,000 or less (107a). As with Medicare, this limit does not include billed charges disallowed by the insurer. The 17 percent of private indemnity beneficiaries without a cap on out-of-pocket expenses would face copayments similar to those borne by Medicare beneficiaries.[22]

Table 9-Selected Insurance Characteristics of Full-Time Participants in Employment-Based Plans at Medium and Large Firms

I. Maximum annual out-of-pocket expense	Percent of beneficiaries
No specified maximum	17?40
$100-$699	19
$700-$1,299	38
$1 ,300-$2,099	16
$2,100 or more	8
Based on earnings	2
	100

II. Lifetime maximum benefits	Percent of beneficiaries
<$500,000	14%
=$500,000	12
$500,001-$999,999	3
= $1,000,000	40
>$1,000,000	2
No lifetime maximum benefits	21
Policy has both lifetime and annual maximums; lifetime maximum not given	6
Total	100

SOURCE: U.S. Department of Labor, Bureau of Labor Statistics, *Employee Benefits in Medium and Large firms, 1989,* Bulletin 2363 (Washington, DC: U.S. Government Printing Office, 1990).

Medicaid and HMO beneficiaries, who represent about 22 percent of all current alglucerase recipients, face little to no out-of-pocket expense. Under some circumstances, States may charge the Medicaid beneficiaries minimal copayments (usually under $5.00) for physician visits and outpatient drugs (112). Many HMOs also require a copayment (usually under $10) for each physician visit (60).[23]

21 For alglucerase patients on Medicare, balance billing applies only to ancillary costs associated with the therapy because HCFA pays the actual cost or average wholesale price (rather than an ''allowed charge' for the drug itself) (107a).

22 According to the U.S. Department of Labor estimates, 80 percent of people with employment-based k-cc from medium and large firms have a 20 percent copayment rate (after paying any annual deductibles), 4 percent face a 15 percent copayment rate, 8 percent face a 10 percent copayment rate, and the remaining 7 percent have some other or no copayment rate (118). Genzyme claims that 92 percent of its non-Medicare, non-Medicaid privately insured customers as of March 1992 had faced a 20 percent copayment or less after meeting an annual deductible (107a).

'Taking $10 as a maximum likely copayment per infusion and assuming a maximum annual number of infusions of 144 (according to the dosing regimen being tested at the Scripps clinic), the maximum potential out-of-pocket expenses for HMO patients would be $1,440. With only two infusions per month (as tested at NIH and Mount Sinai Medical Center in New York City), the maximum out-of-pocket expenses would fall to $240 per year.

Threats to Lifetime Maximum Insurance Benefits

The vast majority of private health insurance policies impose a lifetime limit on the benefits payable for each insuree. According to recent U.S. Department of Labor estimates, at least 26 percent of beneficiaries of private employment-based insurance plans at medium and large firms have a lifetime maximum benefit of $500,000 or less and another 43 percent have a maximum benefit between $500,001 and $1 million (table 9). Genzyme indicated that as of March 1992, only 54 percent of its privately insured customers had a maximum of $1 million or less while 39 percent had no lifetime maximum at all.[24] The high cost of alglucerase therapy puts many Gaucher patients at risk of reaching these lifetime maximum benefits within a few years. Furthermore, Genzyme has indicated that many of its customers have begun therapy with their lifetime maximum benefit already significantly eroded, hastening the termination of their insurance coverage. By exhausting their insurance benefits, patients would not only lack coverage for future alglucerase therapy, but they would have no coverage for any other medical expenses they incur over the rest of their lives. Although Genzyme's free drug program (discussed in the next section) would cover the cost of future alglucerase, it would not pay for the drug's administration or any other medical expenses.

Figure 1 shows how the four different dosing regimens laid out in table 7 would use up lifetime insurance benefits. Even conservatively assuming that patients must pay $2,000 annually toward their alglucerase therapy and that they have no previous medical expenses, all four dosing regimens would significantly erode or completely use up a $500,000 maximum within a few years. A 60 units/kg weekly dose would use up a $1 million maximum in less than two years, while a 60 units/kg biweekly dose reduced to 30 units/kg biweekly after the first year would use up over $800,000 in benefit in less than 5 years. If patients have incurred significant medical expenses prior to beginning alglucerase therapy (as Genzyme indicates is the case), they risk exhausting their insurance benefits even more quickly.

Insofar as 71 percent of current alglucerase recipients have some form of private health insurance, and assuming that between 54 percent (Genzyme's estimate) and 69 percent (U.S. Department of Labor's estimate) of them have a lifetime maximum benefit of $1 million or less, somewhere between one-third and one-half of all aglucerase recipients face a significant risk of exhausting or critically reducing their available insurance benefits over time. Although patients may change health insurers as they change jobs or as their employers change insurance contracts (and hence, receive a ''new' lifetime maximum), in many cases, the new insurance policies may exclude any expenses for Gaucher treatment as a preexisting condition (58).[25] These constraints may also lock Gaucher patients into their current jobs for fear of losing needed health insurance coverage. In addition, even if an employer's insurance does not exclude preexisting conditions, some firms may be unwilling to hire Gaucher patients for fear that the high cost of alglucerase therapy and related medical expenses will lead to higher insurance premiums for the firm as a whole.

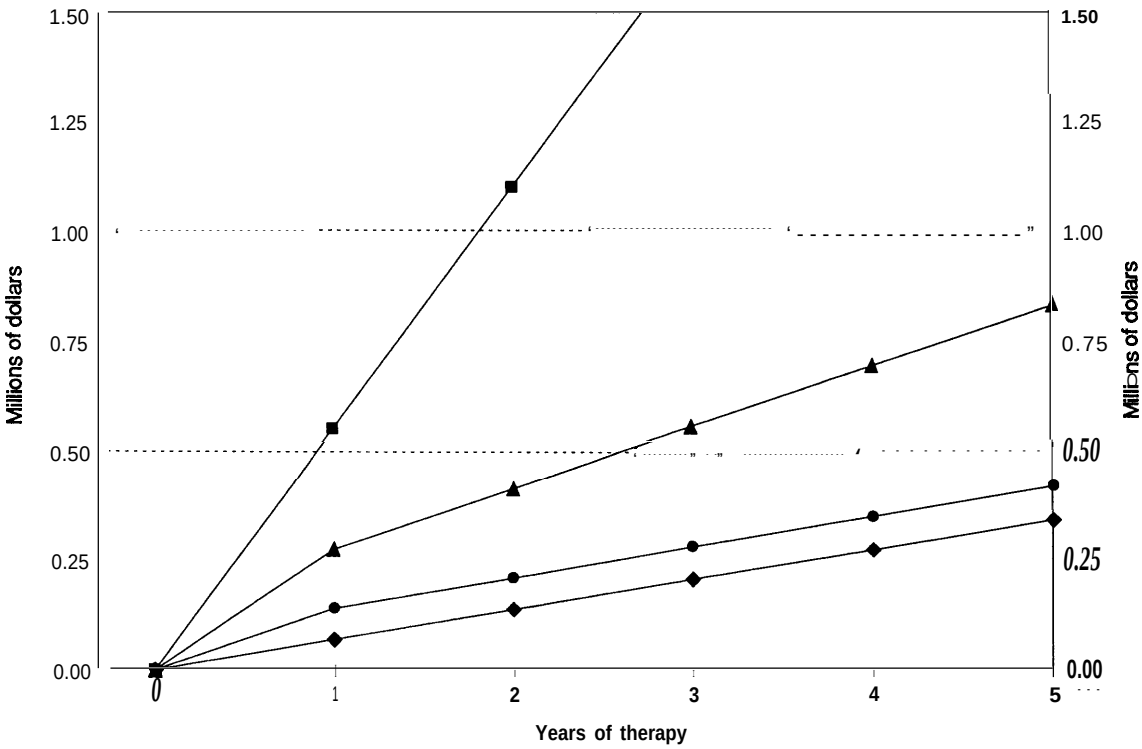
Genzyme's Drug Access Program

Genzyme maintains a staff of "reimbursement specialists" to help patients determine the extent of their insurance coverage for alglucerase therapy, to obtain payment for alglucerase-related expenses, and, if necessary, to help find providers willing to administer the therapy (3). In addition, Genzyme has established a program to provide alglucerase free to Gaucher patients who lack health insurance to cover the therapy or who have reached their lifetime maximum benefits. However, the free drug program does not cover the ancillary costs of alglucerase therapy. As shown in table 7, these costs can range from $4,800 to $13,200 for the average patient. When patients cannot afford these substantial charges, either they or Genzyme must find providers willing

24 Some of the difference between the Department of Labor and Genzyme figures may reflect the fact that the Genzyme figures include the 17 percent of alglucerase recipients enrolled in the Federal Government employees' insurance program and HMOS, which have traditionally not had lifetime maximum benefits (3).

25 Many States allow insurance companies to exclude either particular preexisting conditions or individual patients who have preexisting conditions from coverage when an employer changes insurance contracts. Federal law allows firms that self-insure to make such exclusions no matter what the relevant State's statute requires. Such exclusions are most commonly found among small employers. Insurers can also exclude preexisting conditions for new employees, although a growing number of States are considering legislation to end this practice (58).

Figure l-Cumulative Per Patient Insurance Costs for Alglucerase Therapy Under Four Potential Dosing Regimens[a]



Dosing Regimen A--all 5 years: 60 units/kg weekly

Dosing Regimen B -- first year:60 units/kg biweekly; subsequent years: 30 units/kg biweekly

Dosing Regimen C--first year: 30 unit/kg biweekly; subsequent years:15 units/kg biweekly

Dosing Regimen D -- all 5 years: 2.3 units/kg three times a week

[a]**Assumes patient out-of-pocket expenses of** *$2,000* **per year and treatment costs as outlined** in table 8.

SOURCE: Office of Technology Assessment, 1992.

to administer the therapy at reduced or no compensation.

This program establishes two prices for alglucerase: a price of $3.50/unit for patients with insurance or other resources, and a price of zero for those who cannot pay. By charging insurers the full price, Genzyme has substantial revenue and, at least until they exhaust their lifetime medical benefits, covered patients have access to the therapy and to ancillary services.

It is not uncommon for pharmaceutical companies to charge different payers different prices. This strategy, which economists call price discrimination, can maximize profits. Price discrimination can only occur when a monopolist is able to establish different prices for different buyers. The rationale is straightforward: buyers vary in their willingness or ability to pay for drugs and other products. If the drug manufacturer or other producer can set a higher price for buyers who are willing to pay more, the revenues will be greater than if all buyers must pay the same price. It is more profitable to make a sale at a reduced price, as long as the price exceeds the production cost, than not to make a sale at all. Companies usually do not want information about discounted prices made public because other buyers will demand discounts as well, eroding the ability to charge different prices.

Price variation for medical treatments may take unusual forms. One way to price discriminate is to forgive (or fail to pursue aggressively) the patient's share of the price of a drug. The forgone revenues are

sometimes treated as bad debt for accounting purposes. The free drug program may similarly represent a sophisticated form of price discrimination. Although the company loses money on each unit of drug offered free of charge, the policy of charging full price to insurers (who are typically obligated by contract to pay the insured percent of the drug's price for all FDA-approved indications) during the initial treatment period can be profitable. In the context of Genzyme's complete pricing scheme, the free drug program is similar in its consequences to a policy in which patients are offered a lifetime supply of alglucerase treatment in exchange for the value if their remaining insurance coverage and associated copayments. Patients may be willing to pay the full price of alglucerase as long as they have insurance coverage; when coverage ends, they may be willing or able to pay little if any of the cost. If Genzyme had opted against making the drug available for free at the end of insurance coverage, resistance to the pricing among patient advocates would probably have been intense.

Other Issues in Medicare and Medicaid Payment for Alglucerase Therapy

Medicare Coverage of Disabled Individuals—According to estimates provided by Genzyme, approximately half of current alglucerase recipients with Medicare coverage have this Federal insurance because their Gaucher disease has rendered them disabled (3).[26] However, because alglucerase therapy has the potential to eliminate the physical disabilities associated with Gaucher disease, patients could lose their Medicare coverage if the Social Security Administration (SSA) deems them able to work.[27] HCFA anticipates a reduction in the Medicare rolls because of the effectiveness of alglucerase (31). These patients' ability to get private insurance directly from an insurer or through an employer will also be limited because prospective insurers would likely exclude Gaucher treatment from coverage as a "preexisting condition. " Without other resources, these patients will receive alglucerase through Genzyme's free drug program, but they will still bear the expenses of its administration and any other medical expenses related to their Gaucher disease. As of April 1992, one Medicare beneficiary has expressed an interest in returning to work, but has not done so yet (3).

Securing ***Payment and Providers for Medicare Beneficiaries---Genzyme*** and the National Gaucher Foundation report some instances of Medicare carriers rejecting, suspending, or delaying claims for alglucerase (especially during the early months after FDA approval) despite the fact that the carrier covers the therapy (3,40). In addition, Genzyme reports that a few Medicare beneficiaries have had difficulty in finding medical providers to administer alglucerase. Some physicians have been reluctant to purchase and stock the drug in their offices because of its cost. These physicians tend to refer their Gaucher patients to hospital outpatient clinics to receive their infusions. However, some hospitals have also been reluctant to administer the drug because they initially receive only a portion of the Medicare payments to which they are entitled; they receive the balance through a reconciliation process that takes place as long as a year after they administer the drug.[28] Because of the drug's high cost, the difference between initial payments and the amount to which the hospital is ultimately entitled can be substantial (3,123).

Medicaid Rebates—In 1990, Congress enacted legislation (Public Law 101-508) requiring pharmaceutical manufacturers who supply drugs to Medicaid beneficiaries to pay rebates to States according to a formula based on volume of drug supplied under Medicaid and 1) a percentage of the average manufacturer's price or 2) the "best price' offered to any purchaser of the drug (whichever is greater). Drugs administered as part of a physician's office visit are usually exempt from this Medicaid rebate law. HCFA generally grants this exemption by designating the drug with a "J-code" upon recommendation of the HCFA Common Procedure Coding

26 The other half qualify for Medicare because they are over 65 years old.

27 SSA withdraws disability status from any beneficiary known to engage in "substantial gainful activity" which is defined as earning more than $500 per month. SSA also periodically reviews the condition of all 'disabled' people to determine whether they are still unable to work and expects recipients of Federal disability benefits to no@ the Government of any changes in their medical condition or work status (1 17).

28 Although hospitals are entitled to 80 percent of allowed charges for outpatient prescription drugs, their initial reimbursements for drugs are bundled together with reimbursements for other outpatient services and reduced by a hospital specific cost-to-charge ratio calculated by a prescribed methodology using historical data. Hospitals could mark up the cost of alglucerase to recover the 80 percent to which they are entitled more quickly. However, this strategy would lower the cost-to-charge ratio for all future outpatient Medicare reimbursements (3).

System (HCPCS) Committee.[29] HCFA expects to add alglucerase to the list of exempt drugs before 1993 (98). Genzyme currently participates in the Medicaid rebate program and provides rebates to States based on the prices it charges for alglucerase and the volume of drug provided to Medicaid patients as reported by the States. The exact amount of rebates provided by Genzyme to States is considered proprietary information by both HCFA and Genzyme.

POTENTIAL CONSEQUENCES OF FEDERAL SUBSIDIES

Congress's express intent in passing the Orphan Drug Act was to overcome disincentives to invest in new health care technologies. Implicit in the law is a conviction that firms need substantial guarantees of monopoly power and subsidy of research costs in order to undertake risky and expensive drug development for rare conditions. Drug development is a risky process. Drug companies bear costs for a large number of unsuccessful projects. Therefore, overall profitability requires a relatively high return to the projects that are successful. If high development costs and risks of failure make high returns an essential incentive to invest, high prices may be necessary for companies to make such drugs available. As shown earlier in the paper, other Federal involvement, like NIH research, also helps make the development and provision of pharmaceuticals more attractive to industry.

To those who will pay for alglucerase and to those who are interested in controlling health care expenditures in general, the price of alglucerase and its cost of production are subjects of keen interest. According to Genzyme, the drug has high production costs due to an unusually intensive manufacturing process and expensive material inputs; treatment of one moderately to severely ill adult for a year can require 10 tons of placental material (107). Furthermore, the existence of public and private insurance distorts the individual's decision to undergo treatment. It does so by breaking the link between payment and consumption of health care. Because insured patients do not pay the actual cost of the drug, they (and their physicians) may not be deterred by its cost. Economic theory suggests that in this situation-a monopoly market in which production costs are high and demand does not vary substantially with price-a high price is inevitable. With other pharmaceutical products, the structure of demand is similar, but production costs usually are much lower. This may explain why alglucerase therapy is relatively expensive compared with most medical technologies.

Another important question for policymakers is whether alglucerase injections are worth their cost. From the perspective of moderately to severely ill Gaucher patients, who have had very limited therapeutic options in the past, the answer maybe clear. However, from the perspective of society as a whole which must allocate limited health care resources, this is a serious and difficult question. The limited experience to date strongly suggests that alglucerase reduces the morbidity of moderately to seriously ill Type 1 Gaucher disease, but its effects on mortality are essentially unknown. Even if Gaucher disease were uniformly and rapidly fatal, and alglucerase eliminated all mortality due to the disease, it would still cost up to $350,000 for each year of adult life saved. At this price, alglucerase is not only one of the most expensive treatments ever introduced, but its cost per year of life saved (or per year of life saved adjusted for the quality of that life) would be well above the range of commonly accepted therapies (100). If it does not affect mortality, then any enhancement in the quality of life comes at even greater cost to society.

A related question is whether granting orphan status to the placental form of alglucerase delayed the development of alternative treatments that may have been superior to placental alglucerase in terms of cost, efficacy, or safety. The newly developed recombinant form of alglucerase may be less costly to manufacture (20). Furthermore, Genzyme has claimed that the recombinant form is less likely to be contaminated with viruses than the placental form (107).

However, the placental form of alglucerase may have developed first because the development of recombinant technology often poses greater financial risk to the manufacturer than conventional chemical purification and synthetic techniques. In the presence of this uncertainty, Genzyme may have devoted its initial efforts toward a less efficient but

29'MMdly, the HCPCS committee establishes five-digit codes for procedures provided to Medicare and Medicaid patients. All injectable drugs, including those exempt from the rebate law, have HCPCS codes that begin with the letter "J" (98).

more predictable production technique. If so, it is natural to ask whether Genzyme's orphan protection for its placental product delayed development of less costly recombinant technology. In addition, other manufacturers may have delayed research into recombinant technology if they believed that the original FDA market exclusivity awarded to alglucerase would exclude their own recombinant form of the enzyme (21) or given Genzyme a natural advantage in achieving FDA approval and market exclusivity for its recombinant form. If so, the granting of orphan designation to the alglucerase may have deterred the development of a less expensive manufacturing process.

CONCLUSION

In the case of alglucerase, Federal policy, in combination with insurance reimbursement policies, helped to create and promote a therapy that is very effective, very costly, and potentially very profitable. The Federal role was multifaceted. NIH performed or financed most of the research leading to the discoveries of the enzyme defect that caused Gaucher disease, the infeasibility of treatment with the naturally occurring enzyme, and the structure of alglucerase. NIH licensed its process for the recombinant form of alglucerase to Genzyme and another company. It also performed or funded much of the clinical research that produced evidence regarding effectiveness of treatment, and that helped establish dosing guidelines. Through a series of contracts, NIH has purchased alglucerase from Genzyme in order to carry out these trials and to perform further studies. Thus the Federal Government supported or performed much of the research that made it possible to develop this unique treatment for Gaucher disease, and removed much of the risk that pharmaceutical companies face when they decide to develop a drug.

Another government agency, the FDA, also played a critical role in making alglucerase available to patients *with* Gaucher disease. Although the FDA is sometimes portrayed as an obstacle to pharmaceutical innovation, in this case, the FDA, in administering provisions of the Orphan Drug Act, gave Genzyme a 7-year monopoly in the sale of alglucerase. Because alglucerase had been discovered by NIH, which had published its structure, and because the NIH held a patent for the purification process, Genzyme could not rely upon patent protection for a monopoly position. Without the market exclusivity provision of the ODA, there would have been no monopoly, and the revenues and profits from the sale of alglucerase would presumably have been more modest. The orphan drug law and the NIH's involvement together significantly reduced the cost and uncertainty customarily associated with a manufacturer's pharmaceutical development project.

Genzyme could not maintain the very high price of alglucerase if insurance companies did not pay for the therapy. In fact, most insurers-including the Medicare program administered by the Federal Government and the Medicaid program administered jointly by the Federal Government and the States—are bound by their contractual obligations to cover drugs administered according to FDA-approved labeling. Most private insurance policies place a limit on lifetime benefits, and patients with severe forms of Gaucher disease who receive alglucerase may exhaust their insurance coverage in a few years. At that time, Genzyme will supply the drug without payment, but patients will no longer be covered for their remaining health care, including the costs of administering alglucerase as an intravenous infusion.

The commercial development of alglucerase is unusual insofar as the company that produced it was able to obtain a monopoly in the production of a compound that had already been discovered and for which much of the development work had been performed by the Federal Government and other researchers. Furthermore, it is not representative of all drug development; this is an unusually successful and profitable product. Nevertheless, it raises questions that are common to many new products: What is the appropriate Federal role in the development of a commercial product? Should the potential costs of the product be considered when the Federal Government supports basic and applied research, especially if the Federal Government is itself a payer of such therapies through its own health insurance programs? How should the Federal Government consider impacts on patients and insurers when supporting such work? As the range of new therapeutic products expands, with the promise of unprecedented effectiveness and expense, such questions will arise more and more often. The costs of new diagnostic procedures and treatments may be so high that insurers cannot cover them and patients cannot pay for them. Furthermore, this case illustrates that such deep involvement of agencies such as NIH in the development of medical technology creates the

potential for the Federal Government to pay for such technologies twice-once through support of the R&D process and again as a health insurer. The Federal Government has no mechanism to ensure that the process American pay for drugs and other technologies reflect the public's contribution to their development.

Perhaps the most significant lesson to emerge from the case of alglucerase is that cost considerations cannot be ignored in the development and diffusion of any treatment. Payments for alglucerase, like expenditures for any other treatment ordiagnostic procedure, divert health care resources from other uses. Less expensive treatments, however, are unlikely to attract comparable scrutiny from insurers, and few other treatments will so predictably deplete insurance coverage. The high price of alglucerase threatens to put this promising treatment out of reach of many patients, even those who are well-insured.

REFERENCES

1. Abraharnov, A., Hadas-Halpem, L, Levy-Lahad, E., et al., "Enzyme Replacement Therapy for Children With Gaucher Disease: Law Dose, High Frequency, Lower Cost, High Efficacy," *Pediatric Research 31:137A, 1992.*
2. *Aerts,* J.M.F.G., Donker-Koopman, W.E., Murray, G.J., **et al.**, "A Procedure for the Rapid Purification in High Yield of Human Glucocerebrosidase Using Immunoaffinity Chromatography With Menoclonal Antibodies,' *'Analytic Biochemistry 154:655-663, 1986.*
3. Aleski, W., Director of Reimbursement, Genzyme Corporation, Boston, MA, personal communications, Feb. 26, 1992, Apr. 1 and 9, 1992, and Sept. 8, 1992.
4. Alster, N., "Henri Termeer's Orphan Drug Strategy," *Forbes 147(11):202-205, 1991.*
5. Aubrey, W., Senior Vice President and Medical Director, Blue Shield of California, San Francisco, CA, personal communication, Mar. 5, 1992.
6. Baker, C., and Kramer, N., "Employer-Sponsored Prescription Drug Benefits," *Monthly Labor Review 114:31-35, 1991.*
7. Barranger, J., Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA, personal communication, Sept. 23, 1991.
8. Barranger, J.A., and Ginns, E.I., "Glucosylceramide Lipidosis: Gaucher Disease," *The Metabolic Basis of Inherited Disease,* 6th Ed., C.R. Scriver, A.L. Beaudet, W.S. Sly, and D. Valle (eds.) (New York, NY: McGraw-Hill, 1989).
9. Barton, N., "Ceredase(Macrophage-TargetedGlucocerebrosidase) for the Treatment of Type 1 Gaucher's Disease," *Proceedings From the Endocrinologic and Metabolic Advisory Committee 1:135-248, 1990.*
10. Barton, N., Chief, Clinical Investigation Section, Developmental and Metabolic Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, personal communications, Sept. 19 and 26, 1991, Dec. 11,1991, Jan. 14 and 21, 1992, Feb. 24,1992, Mar. 16, 1992, and July 14, 1992.
11. Barton, N.W., Brady, R.O., Dambrosia, J.M., et al., "Replacement Therapy for Inherited Enzyme Deficiency-Microphage Targeted Glucocerebrosidase for Gaucher's Disease," New *England Journal of Medicine 324;1464-1470,* **1991.**
12. Barton, N.W., Brady, R.O., Dambrosia, J.M., et al., "Dose-Dependent Responses to Macrophage-Targeted Glucocerebrosidase in a Child With Gaucher Disease," *Journal of Pediatrics 120:277-280,1992.*
13. Barton, N.W., Brady, R.O., Murray, G.J., et al., *letter, New England Journalof Medicine 325:1811, 1991.*
14. Barton, N.W., Furbish, F. S., Murray, G.J., et al., "Therapeutic Response to Intravenous Infusions of Glucocerebrosidase in a Patient With Gaucher Disease," *Proceedings of the National Academy of Sciences USA 87:1913-1916, 1990.*
15. Barton, N.W., Murray, G.J., and Brady, R.O., "Hematological Responses Are Dependent on the Amount of Glucocerebrosidase Administered to Patients With Gaucher's Disease, ''Blood 78:43l~ 1991.
16. Beisel, R., Director of the Division of Medicaid Statistics, Health Care Financing Administration, Baltimore, MD, personal communications, Mar. 30, 1992, and Apr. 1, 1992.
17. Belchelz, P.E., Crawley, J. C.W., Braichman, I.P., et al., G., "Treatment of Gaucher's Disease With Liposome-Entrapped Glucocerebrosidase: B Glucosidase," *Luncet* 11:116-117, 1977.
18. Beutler, E., "Gaucher Disease," *Blood Reviews 2:59-70, 1988.*
19. Beutler, E., "Monocyte and Microphage Disorders: Lipid Storage Disorders," Hematology, 4th Ed., W.J. Williams, E. Beutler, A.J. Erslev, and M.A. Lichtman (eds.) (New York NY: McGraw-Hill, 1990).
20. Beutler, E., "Gaucher's Disease," *New England Journal of Medicine 325:1354-1360, 1991.*
21. Beutler, E., Chairman Department of Molecular and Experimental Medicine, Scripps Research Institute, La Jolla, CA, personal communications,

Oct. 22, 1991, Jan. 27, 1992, Feb. 26, 1992, Mar. 24, 1992, and May 29, 1992.

22. Beutler, E., "Gaucher Disease: New Molecular Approaches to Diagnosis and Treatment," *Science 256:794-799, 1992.*
23. Beutler, E., Dale, G.L., Guinto, E., and Kuhl, W., "Enzyme Replacement Therapy in Gaucher's Disease: preliminary Clinical Trial of a New Enzyme Preparation," *Proceedings of the National Academy of Sciences USA 74:4620-4623, 1977.*
24. Beutler, E., Dale, G.L., and Kuhl, W., "Replacement Therapy in Gaucher Disease, *Enzyme Replacement Therapy in Genetic Diseases: 2,* J. Desnick (ed.) (New York, NY: Alan R. Liss, Inc., 1980).
25. Beutler, E., Gelbart, T., Kuhl, W., Serge, J., et al., "Identification of the Second Common Jewish Gaucher Disease Mutation Makes Possible Population-Based Screening for the Heterozygous State,' *Proceeding of the National Academy of Sciences USA 88:10544-10547, 1991.*
26. Beutler, E., Gelbart, T., Kuhl, W., et al., "Mutations in Jewish Patients With Gaucher Disease," *Blood* 79:1662-1666, 1992.
27. Beutler, E., Kay, A., Saven, A., et al., "Enzyme Replacement Therapy for Gaucher Disease,' *Blood 78:1183-1190, 1991.*
28. Beutler, E., Kay, A., Saven, A., et al., letter, New *Journal of Medicine 325:1809-1810, 1991.*
29. Beutler, E., and Saven, A., "Misuse of Marrow Examination in the Diagnosis of Gaucher Disease," *Blood 76:646-648, 1990.*
30. Blitz, M., Vice President of Medical Policy and Research, Blue Cross and Blue Shield of New York, New York, NY, personal communication, Mar. 30, 1992.
31. Booth, C., Director of Office of Payment Policy, Health Care Financing Administration, Baltimore, MD, personal communications, Oct. 3, 1991 and June 17, 1992.
32. Brady, R., Developmental and Metabolic Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, personal communication, Jan. 14, 1992.
33. Brady, R.O., and Barranger, J.A., "Glucosylceramide Lipidosis: Gaucher's Disease," *The Metabolic Basis of Inherited Disease,* 5th Ed., J.B. Stanbury, J.B. Wyngaarden, D.S. Fredrickson, et al. (eds.) (New York, NY: McGraw-Hill, 1983).
34. Brady, R. O., Barranger, J.A., Furbish, F. S., et al., "Prospects for Enzyme Replacement Therapy in Gaucher Disease,' *Gaucher Disease: A Century of Delineation and Research,* R.J. Desnick, S. Gatt, and G.A. Grabowski (eds.) (New York, NY: Alan R. Liss, Inc., 1982).
35. Brady, R. O., Barranger, J. A., Gal, A. E., et al., "Status of Enzyme Replacement Therapy for Gaucher Disease," *Enzyme Therapy in Genetic Diseases: 2,* R.J. Desnick (cd.) (New York, NY: Alan R. Liss, Inc., 1980).
36. Brady, R.O., Dambrosia, J.M., Barton, N. W., "Effectiveness of Low-Dose Replacement Therapy in Gaucher's Disease, ' *Clinical Research 40:144A, 1992.*
37. Brady, R. O., Pentchev, P. G., Gal, A. E., et al., "Replacement Therapy for Inherited Enzyme Deficiency. Use of Purified Glucocerebrosidase in Gaucher's Disease," New *England Journal of Medicine 291:989-993, 1974.*
38. Chirnoff, A., Medica Health Plan of United Health Care, Minneapolis, MN, personal communication, Mar. 30, 1992.
39. Choy, F.Y.M., "Purification of Human Placental Glucocerebrosidase Using a Two-Step High-Performance Hydrophobic and Gel Permeation Column Chromatography Method,' *Analytic Biochemistry 156:515-520, 1986.*
40. Cohen, K., Executive Director, National Gaucher's Foundation, Gaithersburg, MD, personal communication, Apr. 13, 1992.
41. Cohen, L., Medical Director, Blue Cross and Blue Shield of Virginia, Richmond, VA, personal communication, Mar. 31, 1992
42. Comanor, W. S., "The Political Economy of the Pharmaceutical Industry," *Journal of Economic Literature 24:1178-1217, 1986.*
43. *Consumer Reports,* "Beyond Medicare," *Consumer Reports 54(6):375-391,* June 1989.
44. Dale, G. L., and Beutler, E., "Enzyme Replacement Therapy in Gaucher's Disease: A Rapid High-Yield Method for Purification of Glucocerebrosidase," *Proceedings of the National Academy of Sciences USA 73;4672-4674, 1976.*
45. Dale, G. L., Beutler, E., Fournier, P., et al., "Large Scale Purification of Glucocerebrosidase From Human Placentas," *Enzyme Therapy in Genetic Diseases: 2,* R.J. Desnick (cd.) (New York, NY: Alan R. Liss, Inc., 1980).
46. Dennally, J., Medical Director, Blue Cross and Blue Shield of Connecticut, North Haven, CT, personal communication, Mar. 26, 1992.
47. DiMasi, J. A., Hansen, R.W., Grabowski, H. G., et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics 10:107-142, 1991.*
48. Doebber, T.W., Wu, M. S., Bugianesi, R.L., et al., "Enhanced Microphage Uptake of Synthetically Glycosylated Human Placental Beta_Glucocerebrosidase," *Journal of Biological Chemistry 257:2193-2199, 1982.*

49. Ebert, K.M., Selgrath, J.P., DiTullio, P., et al., "Transgenic Production of a Variant of Human Tissue-type Plasminogen Activator in Goat Milk: Generation of Transgenic Goats and Analysis of Expression," *Biotechnology 9:835-838, 1991.*

50. Erikson, E., Groth, G. C., Mansson, J.E., et al., "Clinical and Biochemical Outcome of Marrow Transplantation for Gaucher Disease of the Norrbottnian Type," *Acta Paediatrica Scandanavica 79:680-685, 1990.*

51. Eyal, N., Wilder, S., and Horowitz, M., "Prevalent and Rare Mutations Among Gaucher Patients," *Gene **96:277-283, 1990.***

52. Fallet, S., Grace, M.E., Sibille, A., et al., "Enzyme Augmentation in Moderate to Life-Threatening Gaucher Disease," *Pediatric Research 31:496-502, 1992.*

53. Figueroa M.L., Sate, Y., Kay, A., et al., "Efficacy of Frequently Administered Macrophage-Targeted Glucocerebrosidase in the Treatment of Gaucher Disease," *Clinical Research 40:167A, 1992.*

54. Fink, J.K., Correll, P.H., Perry, L.K., et al., "Correction of Glucocerebrosidase Deficiency After Retroviral-Mediated Gene Transfer Into Hematopoietic Progenitor Cells From Patients With Gaucher Disease," *Proceedings of the National Academy of Sciences USA 87:2334-2338, 1990.*

55. Ford, M., *Medicaid: Reimbursement for Outpatient Prescription Drugs,* Congressional Research Service Report to Congress No. 91-235 EPW (Washington, DC: U.S. Government Printing Office, 1991).

56. Furbish, F. S., Blair, H.E., Shiloach, J., et al., "Enzyme Replacement Therapy in Gaucher's Disease: Large-Scale Purification of Glucocerebrosidase Suitable for Human Administration," *Proceedings of the National Academy of Sciences* USA 74:3560-3563, 1977.

57. Furbish, F. S., Steer, C.J., Krett, N.L., et al., ''Uptake and Distribution of Placental Glucocerebrosidase in Rat Hepatic Cells and Effects of Sequential Deglycosylation," *Biochimica et Biophysics Acta 673:425-34, 1981.*

58. Gauthier, A.K., Associate Director, Alpha Center, Washington, DC, personal communication, Sept. 8, 1992.

59. Genzyme Corporation, Annual Report and Form 1O-K, Filings With the U.S. Security Exchange Commission, Washington, DC, 1987 to 1990.

60. Gold, M., and Hodges, D., *HMO Industry Profile, Volume 1: Benefits, Premiums, and Market Structure in 1990* (Washington, DC: Group Health Association of America, 1991).

61. Grabowski, G., Professor, Department of Genetics and Molecular Biology, Mount Sinai Medical Center, New York, NY, personal communications, Sept. 17, 1991, Jan. 15 and 28, 1992, and June 1, 1992.

62. Grabowski, G.A., and Dagan, A., "Human Lysosomal B-Glucosidase: Purification by Affinity *Chromatography, ''Analytic Biochemistry 141:267-279,1984.*

63. Grabowski, G.A., Gatt, S., and Horowitz, M., "Acid B-Glucosidase: Enzymology and Molecular Biology of Gaucher Disease,' *Critical Reviews in Biochemistry and Molecular Biology 25:385-414,1990.*

64. Gregoriadis, G., Neerunjun, D., Meade, TW., et al., "Experiences After Long-Term Treatment of a Type 1 Gaucher Disease Patient With Liposome-Entrapped Glucocerebroside: B-Glucosidase," *Enzyme Therapy in Genetic Diseases: 2,* R.J. Desnick (cd.) (New York, NY: Alan R. Liss, Inc., 1980).

65. Gribble, T.J., and Latimer, K., "Successful Use of Enzyme Therapy in Gaucher's Disease" [abstract no. 556], *American Journal of Human Genetics 49:113, 1991.*

66. Groth, C.G., Collste, H., Dreborg, S., et al., "Attempt at Enzyme Replacement by Organ Transplantation; Renal Transplantation in Gaucher's Disease," *Transplantation Proceedings 11:1218-1219, 1979.*

67. Groth, C.G., Dreborg, S., Oeckerman, P.A., et al., "Splenic Transplantation in a Case of Gaucher's Disease," *Lancet* I:260-1264, 1971.

68. Hansen, R., "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effect of Proposed Regulatory Changes,' *Issues in Pharmaceutical Economics,* R.A. Chien (cd.) (Lexington, MA: D.C. Heath and co., 1979).

69. Hessen, J., Administrator of Pharmacy, Policy and Education, Aetna Insurance, personal communication, Mar. 31, 1992.

70. Hickman, W., Director of the Office of Medicaid Policy, Health Care Financing Administration, personal communication, Mar. 24, 1992.

71. Hobbs, J.R., Shaw, P.J., Hugh-Jones, K., et al., ''Beneficial Effect of Pre-Transplant Splenectomy on Displacement Bone Marrow Transplantation for Gaucher's Syndrome," *Luncet* I:1111-1115, 1987.

72. Karson, E.M., "Principles of Gene Transfer and the Treatment of Disease, *Biotechnology 16:189-212, 1991.*

73. Keefe, J., Comptroller, Genzyme Corporation, Boston, MA, personal communications, Feb. 26, 1992 and Sept. 4, 1992.

74. Kirkpatrick, D. V., Barrios, N. J., Shapira, E., et al., "Treatment of Enzyme Storage Disease With Matched and Partially Matched Bone Marrow Transplantation: The Tulane Marrow Transplant Group Experience" [abstract No. 2184], *Blood 76:548A,1990.*
75. Kleinschmidt, T., Christomanou, H., and Braunitzer, G., "Complete Amino-Acid Sequence and Carbohydrate Content of the Naturally Occurring Glucosylceramide Activator Protein (Al activator) Absent From a New Human Gaucher Disease Variant," *Biological Chemistry Hoppe-Seyler 368:1571-1578, 1987.*
76. Klipstein, E., Medical Director, Metropolitan Insurance Company, personal communication, Mar. 27, 1992.
77. Kohn, D, B., Nolta, J.A., and Weinthal, J., "Toward Gene Therapy for Gaucher Disease,' *Human Gene Therapy 2:101-105, 1991.*
78. Krivit, W., "Lysosomal Storage Diseases," *Hematology Basic Principles and Practice, R.* Hoffman, E.J. Benz, S.J. Shattil, et al. (eds.) (New York, NY: Churchill Livingstone, 1991).
79. Krivit, W., "Bone Marrow Transplantation as Treatment for Storage Diseases: Background Review and Specific Application to Gaucher's Disease, ' *Japanese Journal of Inborn Errors of Metabolism, in* press.
80. Latham, T.E., Theophilus, B.D.M., Grabowski, G.A., and Smith, F.I., "Heterogeneity of Mutations in the Acid Beta-Glucosidase Gene of Gaucher Disease Patients,' *DNA and Cell Biology 10:15-21, 1991.*
81. Ludman, M.D., Lipton, J., Sadhev, I., et al., "Gaucher Disease: Bone Marrow Transplantation in Rapidly Progressive Disease' [abstract no. *237], American Journal ofHumanGenetics 43:A60, 1988.*
82. Maltz, D., Vice President of Medical Policy, Blue Cross and Blue Shield of Massachusetts, Boston, MA, personal communication, Mar. 25, 1992.
83. Matoth, Y., Chazan, S., Cnaan, A., et al., "Frequency of Carriers of Chronic (Type 1) Gaucher Disease in Ashkenazi Jews," *American Journal of Medical Genetics 27:561-565, 1987.*
84. McCollam, A., Medical Director, The Prudential Insurance Company, personal communication, Mar. 24, 1991.
85. McDonough, K., Medical Director, Mutual of Omaha, Inc., personal communication, Mar. 24, 1992.
86. McLachlan, D., Senior Vice President and Chief Financial Officer, Genzyme Corporation, Boston, MA, personal communications, Feb. 26,1992, and Sept. 4, 1992.
87. Molyneaux, G., Assistant Medical Director, Blue Cross and Blue Shield of California, San Francisco, CA, personal communication, Mar. 26, 1992.
88. Murray, G. J., "Lectin-Specific Targeting of Lysosomal Enzymes to Reticuloendothelial Cells," *Methods in Enzymology 149:25-42, 1987.*
89. Murray, G.J., Howard, K.D., Richards, S. M., et al., "Gaucher's Disease: Lack of Antibody Response in 12 Patients Following Repeated Intravenous Infusions of Mannose Terminal Glucocerebrosi*dase,''Journal of Immunological Methods 137:1 13-120, 1991.*
90. Murray, G.J., Youle, R. J., Gandy, S. E., et al., "Purification of Beta-Glucocerebrosidase by Preparative-Scale High-Performance Liquid Chromatography: The Use of Ethylene Glycol-Containing Buffers for Chromatography of Hydrophobic Glycoprotein Enzymes," Analytic Biochemist 147:301-130, 1985.
91. Nelson, C., Census Bureau, U.S. Department of Commerce, personal communication, Mar. 26, 1991.
92. Nitkowsky, H. M., Madan, S., and Goldman, H., "Experience With Intravenous Infusions of Glucocerebrosidase in a Patient With Gaucher Disease" [abstract no. 560], *American Journal of Human Genetics,* vol. 49, 1991.
93. Ohashi, T., Marchese, S., Pegram, D., and Barranger, J.A., "Development and Application of a Treatment for Gaucher Disease Using Glucocerebrosidase Targeted to Macrophages" [abstract no. 552], *American Journal of Human Genetics,* vol. 49, 1991.
94. Osiecki-Newman, K. M., Fabbro, D., Dinur, T, et al., 'Human Acid Beta-glucosidase: Affinity Purification of the Normal Placental and Gaucher Disease Splenic Enyzmes on N-alkyl-deoxynojirimycin-sepharose," *Enzyme 35:147-153, 1986.*
95. Pastores, G. M., Sibille, A. R., and Grabowski, G. A., 'Enzyme Augmentation Therapy in Gaucher Disease Type I: Dosage, Efficacy and Adverse Effects," *Clinical Research 40:357A, 1992.*
96. Pentchev, P. G., Brady, R. O., Hibbert, S.R., et al., "Isolation and Characterization of Glucocerebrosidase From Human Placental Tissue, ' *Journal of Biological Chemistry 248:5256-61, 1973.*
97. Rappeport, J.M., Barranger, J.A., and Ginns, E. I., "Bone Marrow Transplantation in Gaucher Disease," *Birth Defects 22:101-109, 1986.*
98. Reed, L., Chief of Medicaid Non-Institutional Payment Policy Branch, Health Care Financing Administration, Baltimore, MD, personal communication, Mar. 26, 1992.
99. Ringden, O., Groth, C. G., Aschan, J., et al., 'Bone Marrow Transplantation for Metabolic Disorders

at Huddinge Hospital,' *Transplantation Proceedings 22:198-202, 1990.*

100. Russell, L.B., "Some of the Tough Decisions Required by a National Health Plan," *Science 240:892-896, 1989.*

101. Shore, R., Vice President of Research, Enzon Inc., Plainfield, NJ, personal communication, July 10, 1992.

102. Short, J., Executive Secretary, Endocrinologic and Metabolic Drugs Advisory Committee, Food and Drug Administration, Washington, DC, personal communication, Oct. 14, 1992.

103. Sorge, J., Kuhl, W., West, C., et al., Complete Correction of the Enzymatic Deficit of Type 1 Gaucher Disease Fibrolasts by Retroviral-mediated Gene Transfer," *Proceedings of the National Academy of Sciences USA 84:906-909, 1987.*

104. Stahl, P.D., Rodman, J.S., Miller, M.J., et al., "Evidence for Receptor-Mediated Binding of Glycoproteins, Glycoconjugates, and Lysosomal Glycosidases by Alveolar Macrophages," *Proceedings of the National Academy of Sciences USA 75:1399-1403, 1978.*

105. Starer, F., Sargent, J.D., and Hobbs, J.R., "Regression of the Radiological Changes of Gaucher's Disease Following Bone Marrow Transplantation," *British Journal of Radiology 60:1189-1895, 1987.*

106. Strasberg, P.M., Lowden, J.A., and Mahuran, D., "Purification of Glucosylceramidase by Affinity Chromatography," *Canadian Journal of Biochemistry 60:1025-1031, 1982.*

107. Taunton-Rigby, A., Vice President of Therapeutics, Henri Termeer, Chief Executive Officer, David McLachan, Treasurer, William Aleski, Director of Reimbursement, Genzyme Corporation, Boston, MA, personal communications, Oct. 20, 1991, Nov. 11,1991, Dec. 6,1991, Feb. 26,1992, and Mar. 10, 1992.

107a. Taunton-Rigby, A., Vice President of Therapeutics, Genzyme Corporation, Boston, MA, personal communication, June 12, 1992.

107b. Taunton-Rigby, A., Vice President of Therapeutics, Genzyme Corporation, Boston, MA, personal communication, Sept. 4, 1992.

108. Theophilus, B., Latham, T., Grabowski, G. A., et al., "Gaucher Disease: Molecular Hetorogenity and Phenotype-genotype Correlations, ' *American Journal of Human Genetics 45:212-225, 1989.*

109. Tsai, P., Lipton, J. M., Sahdev, I., et al., "Allogenic Bone Marrow Transplantation in Severe Gaucher Disease," *Pediatric Research 31:503-507, 1992.*

110. Tsuji, S., Choudary, P.V., Martin, B.M., et al., "A Mutation in the Human Glucocerebrosidase Gene in Neuronopathic Gaucher's Disease,' New *England Journal of Medicine 316:570-575, 1987.*

111. Tsuji, S., Martin, B.M., Barranger, J.A., et al., "Genetic Heterogeneity in Type 1 Gaucher Disease: Multiple Genotypes in Ashkenazic and Non-Ashkenazic Individuals," *Proceedings of the National Academy of Sciences USA 85:2349-2352, 1988.*

112. U.S. Congress, Library of Congress, Congressional Research Service, *Medicaid Source Book: Background Data and Analysis,* Report for the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives, Committee Print 1OO-AA (Washington, DC: U.S. Government Printing Office, 1988).

113. U.S. Congress, Office of Technology Assessment, *Federal Policies and Medical Devices Industry, OTA-H-230* (Washington, DC: U.S. Government Printing Office, 1984).

114. U.S. Congress, Office of Technology Assessment, *Home Drug Infusion Under Medicare,* OTA-H-509 (Washington, DC: U.S. Government Printing Office, 1992).

115. U.S. Congress, Office of Technology Assessment, *Government Policies and Pharmaceutical Research and Development* (Washington, DC: U.S. Government Printing Office, forthcoming).

116. U.S. Department of Health and Human Services, Health Care Financing Administration, *Health Care Financing Program Statistics: Medicare and Medicaid Data Book, 1990,* HCFA Publication No. 03314 (Washington, DC: U.S. Government Printing Office, 1991).

117. U.S. Department of Health and Human Services, Social Security Administration, *Disability,* SSA publication No. 05-10029 (Washington, DC: U.S. Government Printing Office, 1991).

118. U.S. Department of Labor, Bureau of Labor Statistics, *Employee Benefits in Medium and Large Firms, 1989,* Bulletin 2363 (Washington, DC: U.S. Government Printing Office, 1991).

119. Whellam, J., Branch Chief of the Payment Policy Branch, Health Care Financing Administration, Baltimore, MD, personal communication, Apr. 20, 1992.

120. Wren, R., Director of Coverage and Eligibility Policy, Health Care Financing Administration, Baltimore, MD, personal communications, Oct. 3, 1991 and Mar. 24, 1992.

121. Zelliner, J., Medical Adviser, Health Care Financing Administration, Baltimore, MD, personal communications, Oct. 3, 1991 and Mar. 24, 1992.

122. Zimran, A., Gelbart, T., Westwood, B., Grabowski, G. A., and Beutler, E., ''High Frequency of the Common Jewish Mutation for Type 1 Gaucher

Disease Among the Ashkenazi Jewish Population," *Blood* 76:199a, 1991.
123. Zimran, A., Gelbart, T., Westwood, B., et al., "High Frequency of the Gaucher Disease Mutation at Nucleotide 1226 Among Ashkenazi Jews,' *American Journal of Human Genetics 49:855-859, 1991.*
124. Zimran, A., Gross, E., West, C., et al., "Prediction of Severity of Gaucher's Disease by Identification of Mutations at DNA Level, " *Lancet* II:349-352, 1989.
125. Zimran, A., Hadas-Halpern, I., and Abrahamov, A., letter, New *England Journal of Medicine 325:1810-1811, 1991.*