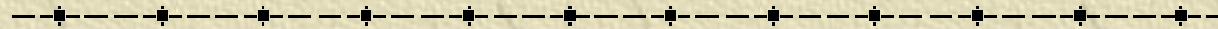


Gaucher Disease

Most Common Lipid-Storage Disease



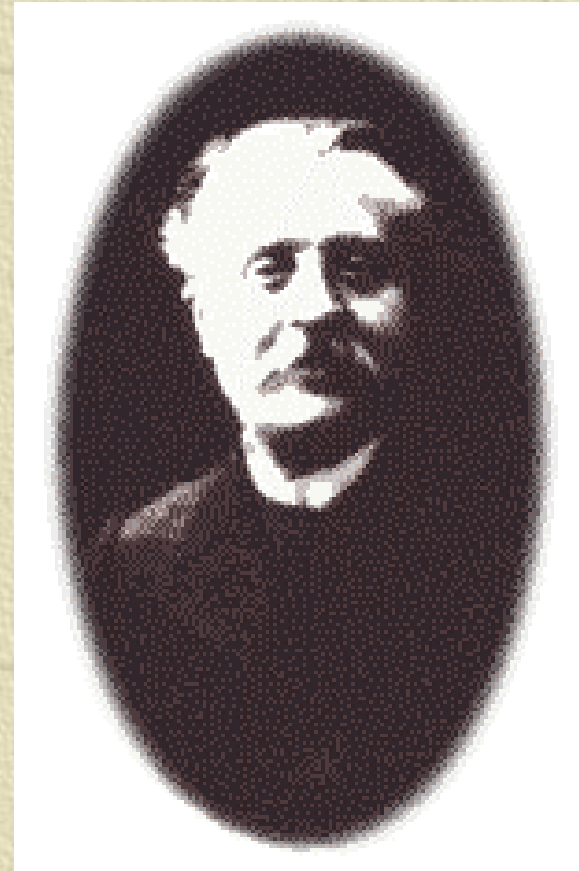
Chris Lemke

Biochemistry/Molecular Biology

April 23, 2001

History of Gaucher Disease

✦ 1882- French physician, Philippe Charles Ernest Gaucher (go-SHAY) described a clinical syndrome in a 32 yr. old woman whose liver and spleen were enlarged.



History of Gaucher Disease

- ✦ 1924- German physician, H. Lieb isolated a particular fatty compound from the spleens of people with Gaucher disease.
- ✦ 1934- French physician, A. Aghion identified this compound as glucocerebroside.
- ✦ 1965- American physician, Roscoe O. Brandy demonstrated that the accumulation of glucocerebroside results from a deficiency of the enzyme glucocerebrosidase.

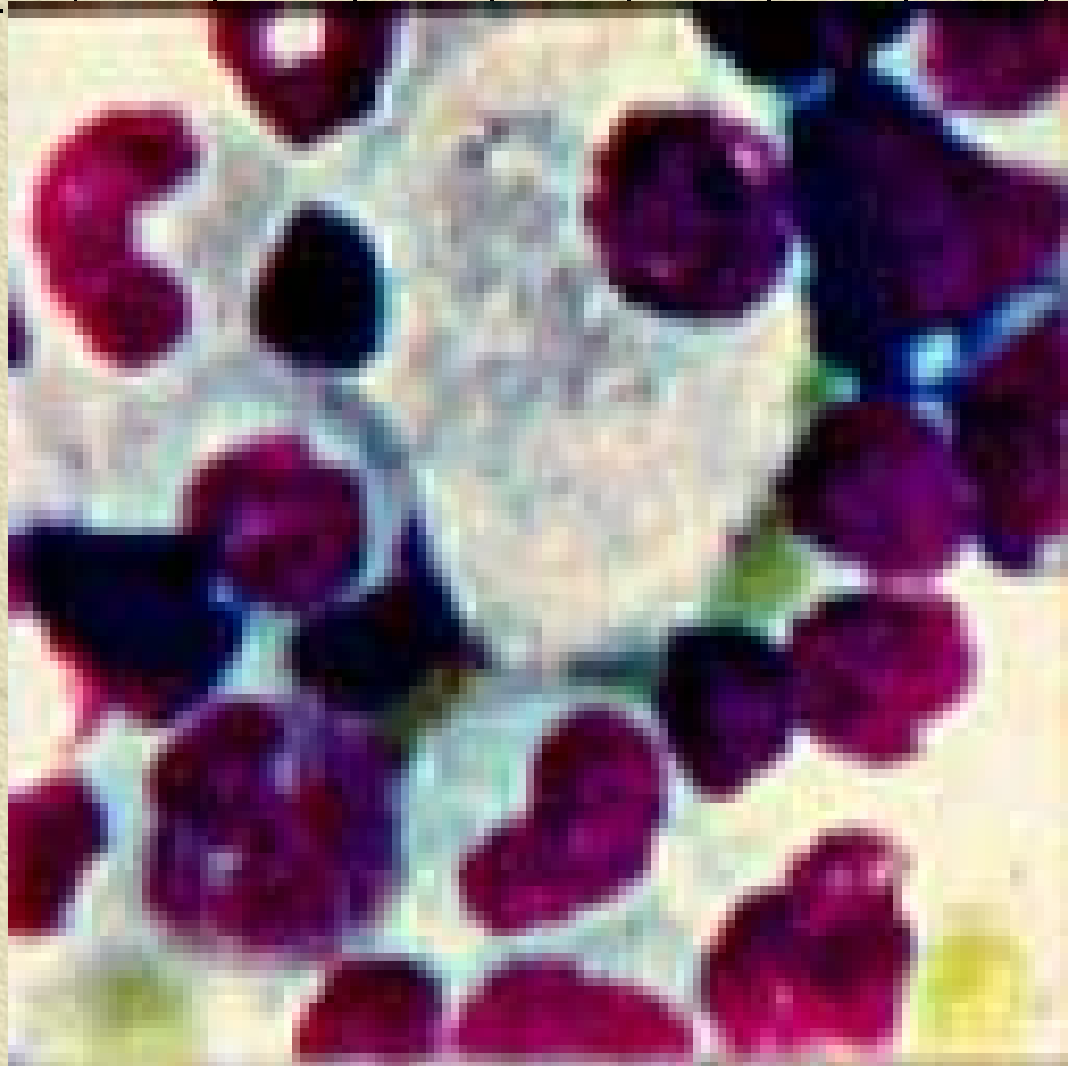
What is Gaucher Disease?

- ✦ The human body contains macrophages that remove worn-out cells by degrading them into simple molecules for recycling.
- ✦ Degradation occurs inside lysosomes.
- ✦ The enzyme glucocerebrosidase is located within the lysosomes and degrades glucocerebroside into glucose and ceramide.

What is Gaucher Disease?

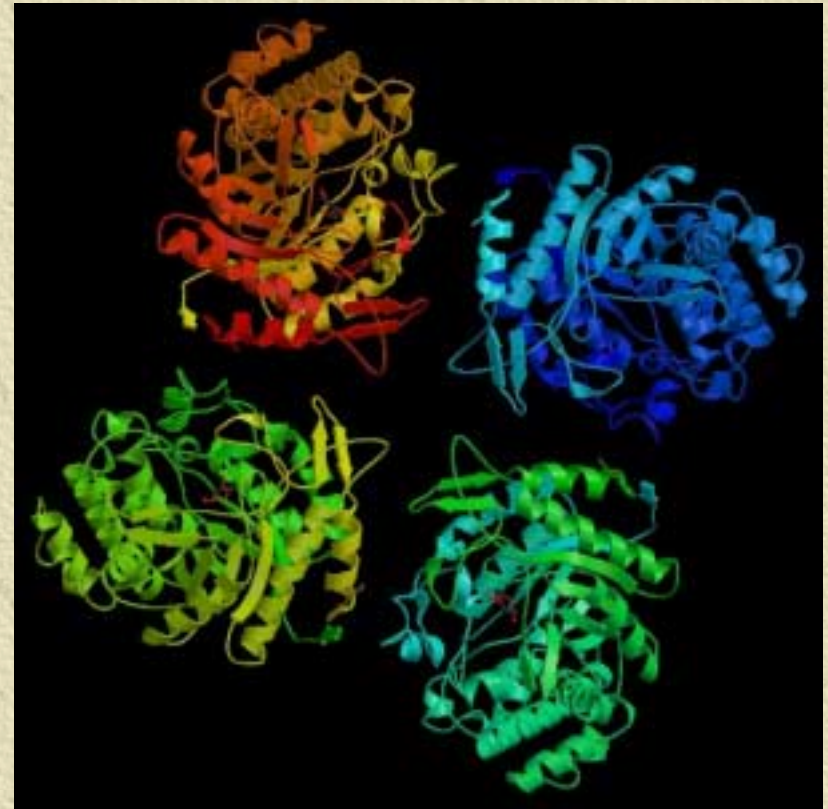
- ✦ People with Gaucher disease lack the normal form of the glucocerebrosidase, and are unable to break down glucocerebroside.
- ✦ Instead, glucocerebroside remains stored within the lysosomes, preventing the macrophages from functioning normally.
- ✦ Enlarged macrophages, due to the accumulated glucocerebroside, are known as, Gaucher cells.

Gaucher Cell



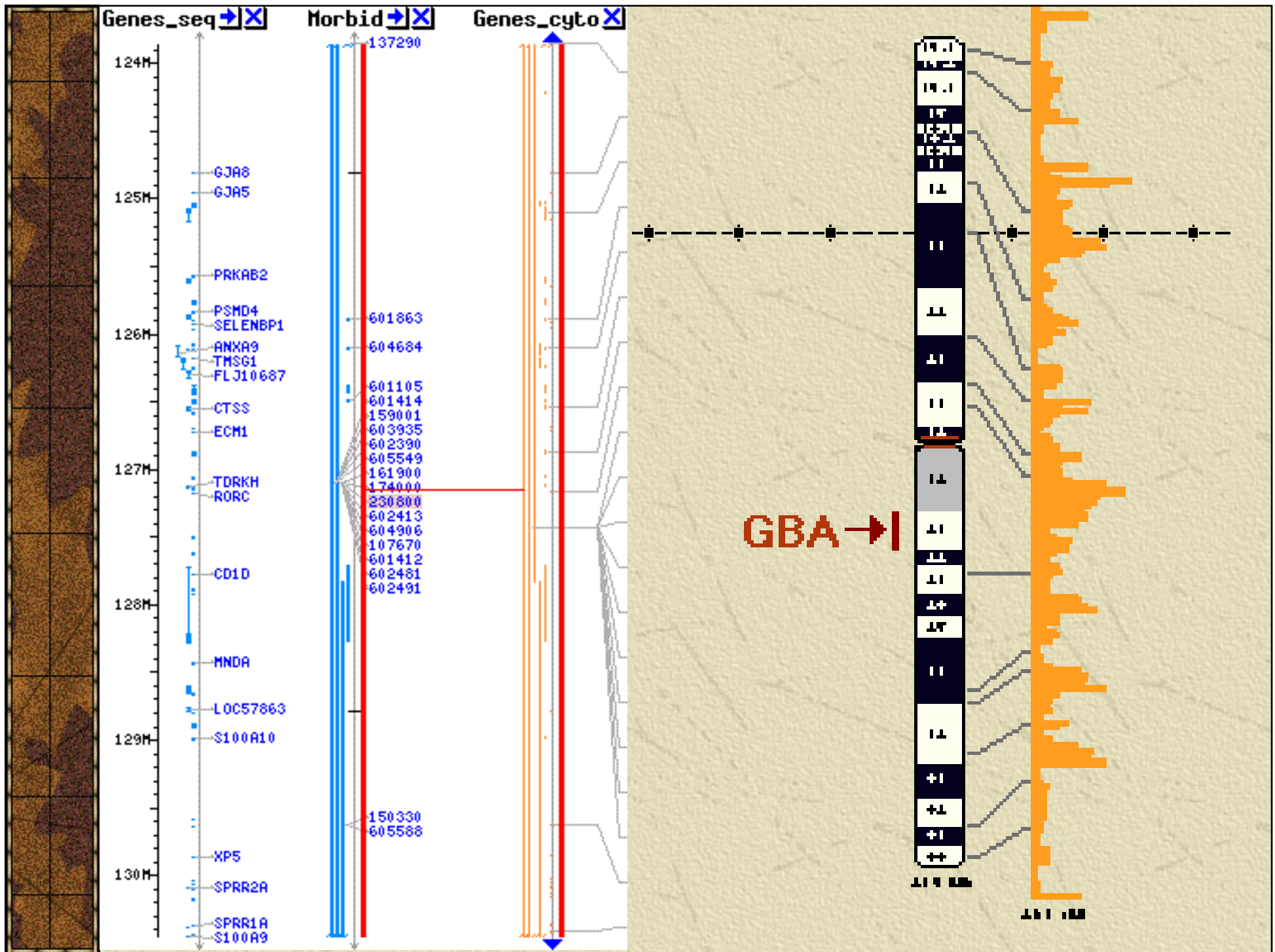
The Enzyme

- ✦ Glucocerebrosidase
- ✦ Molecular weight = 51,637
- ✦ Number of residues = 448
- ✦ Number of alpha = 18
- ✦ Number of beta = 17



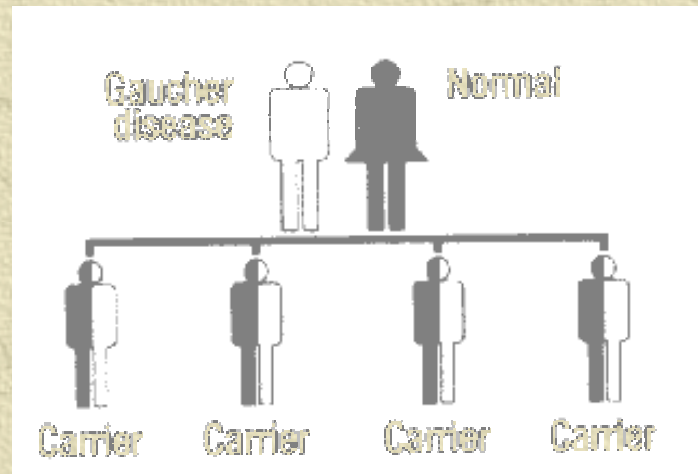
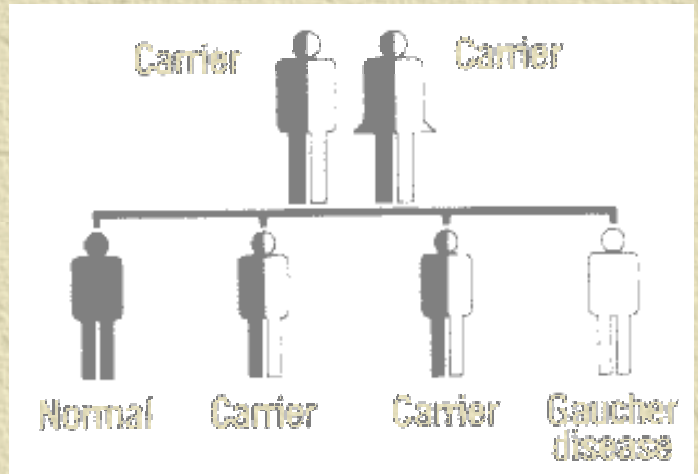
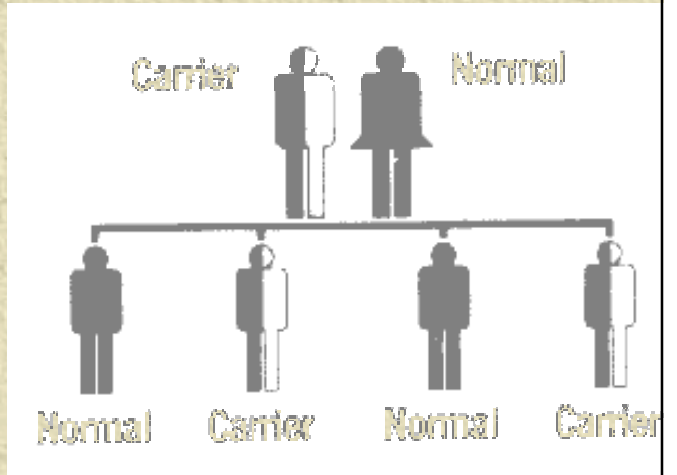
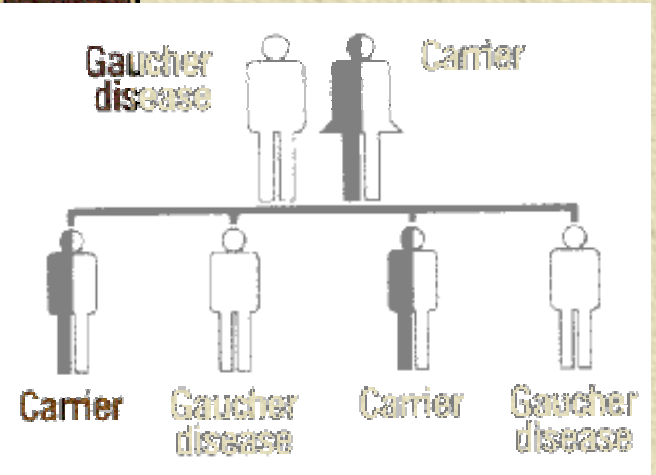
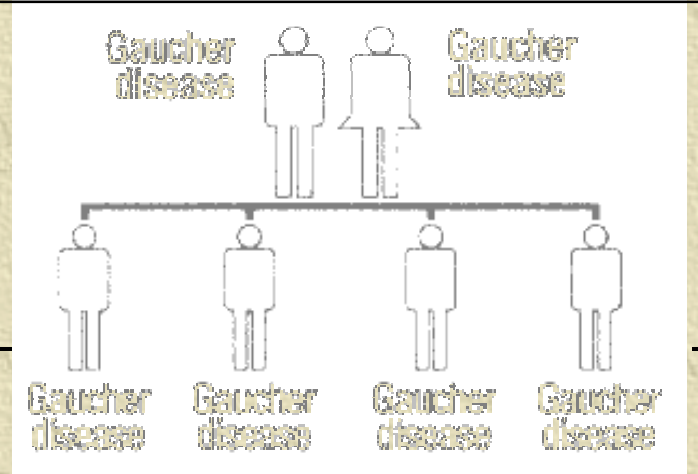
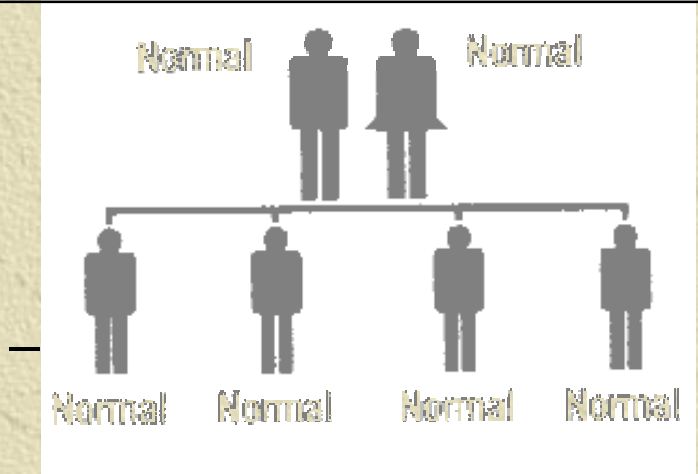
The Mutation

- ✦ Glucocerebrosidase gene locus 1q21
- ✦ Single-base mutation (adenosine to guanosine transition) in exon 9 of the glucocerebrosidase gene.
- ✦ Amino acid substitution of serine for asparagine.
- ✦ Transient expression studies following oligonucleotide-directed mutagenesis of the normal cDNA confirmed that the mutation results in loss of glucocerebrosidase activity.



Inheritance Patterns

- ✦ Gaucher disease is a autosomal recessive trait.
- ✦ Gaucher carriers have have one normal copy of the glucocerebrosidase gene and one defective copy.
- ✦ Since the trait is autosomal, Males and Females have an equal chance of inheriting the defective gene.



Gaucher Diseases

- ✦ Gaucher specialists divide the disease into 3 classifications based on the particular symptoms and course of the disease.
- ✦ Type 1, Adult Gaucher Disease
- ✦ Type 2, Infantile Gaucher Disease (Rare)
- ✦ Type 3, Juvenile Gaucher Disease (Rare)

Type 1, Adult Gaucher Disease

- ✦ Most common form.
- ✦ Defective gene for glucocerebrosidase occurs in 1 in 100,000 people in the general population.
- ✦ More common among Ashkenazi Jews, occurring in 1 in every 850 births.

Type 1 Symptoms

✦ General Fatigue

- ◆ Lack of energy and stamina

✦ Abdomen

- ◆ Enlarged spleen
- ◆ Enlarged liver
- ◆ Pain
- ◆ Compression of the lungs

Type 1 Symptoms

✦ Skeletal System

- ◆ Growth retardation in children
- ◆ Pain and degeneration of joints and bone-covering tissue
- ◆ Loss of bone density leading to widening of the bones along the knee joint
- ◆ Curvature of the bones
- ◆ Spontaneous fractures
- ◆ Acute bone infarctions
- ◆ Bone necrosis

Type 1 Symptoms

✦ Lungs

- ✦ Decreased ability to provide oxygen to the blood

✦ Kidney

- ✦ Disruption of normal function

✦ Skin

- ✦ Yellow-brown pigmentation
- ✦ Non-raised, round, red spots around the eyes.

Type 1 Symptoms

✦ Blood

- ◆ Increased bleeding tendency such as nose bleeds and bruising
- ◆ Sublevels of blood platelets, RBC, WBC.
- ◆ Elevated levels of acid phosphatase and plasma proteins

✦ Digestive

- ◆ Loss of appetite
- ◆ Intestinal complaints.

Treatment: Enzyme Replacement Therapy

- ✦ Most logical, direct therapeutic approach, since people with Gaucher disease are deficient in Glucocerebrosidase.
- ✦ Dr. Roscoe Brady pioneered the development of this therapy at the National Institute of Neurological Disorders and Stroke.

Enzyme Replacement Therapy

- ✦ Research showed natural glucocerebrosidase infusions were ineffective!
- ✦ Dr. Brady developed modified glucocerebrosidase (Ceredase) that had increased targeting and uptake by the macrophages.
- ✦ Ceredase. FDA approval in 1992.

Enzyme Replacement Therapy

- ✦ The production of Ceredase enzyme using a recombinant cell line has been achieved.
- ✦ New name, Cerezyme.
- ✦ Cerezyme received FDA approval in Nov. 1996.
- ✦ Ceredase has been phased out and replaced by Cerezyme for 95% of patients.

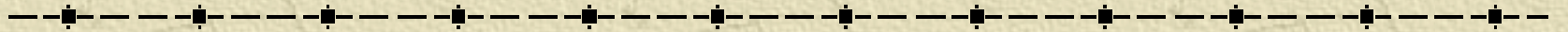
Current Research

- ✦ Investigation of the biophosphonate group of drugs for osteoporosis and bone disease.
 - ◆ Fosamax or Alendronate
 - ◆ Didronel or Etidronate
 - ◆ Pamidronate
- ✦ Attempts to do gene therapy which if successful could provide a cure.
- ✦ Trial of OGT 918
 - ◆ A drug which acts as an inhibitor of one of the key enzymes responsible for the formation of glycosphingolipids such as glucocerebroside.

Summary

- ✦ Gaucher Disease was named after French physician, Philippe Charles Ernest Gaucher (go-SHAY)
- ✦ Most common lipid-storage disorder.
- ✦ Autosomal recessive trait
- ✦ Results from a glucocerebrosidase deficiency, causing an accumulation of glucocerebroside in macrophages.
- ✦ Enzyme replacement therapy is the most logical, direct treatment.

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