Gaucher Disease

Most Common Lipid-Storage Disease

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History of Gaucher Disease

- 1882- French physician, Philippe Charles Ernest Gaucher (go-SHAY) described a clinical syndrome in a 32 yr. old women 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.

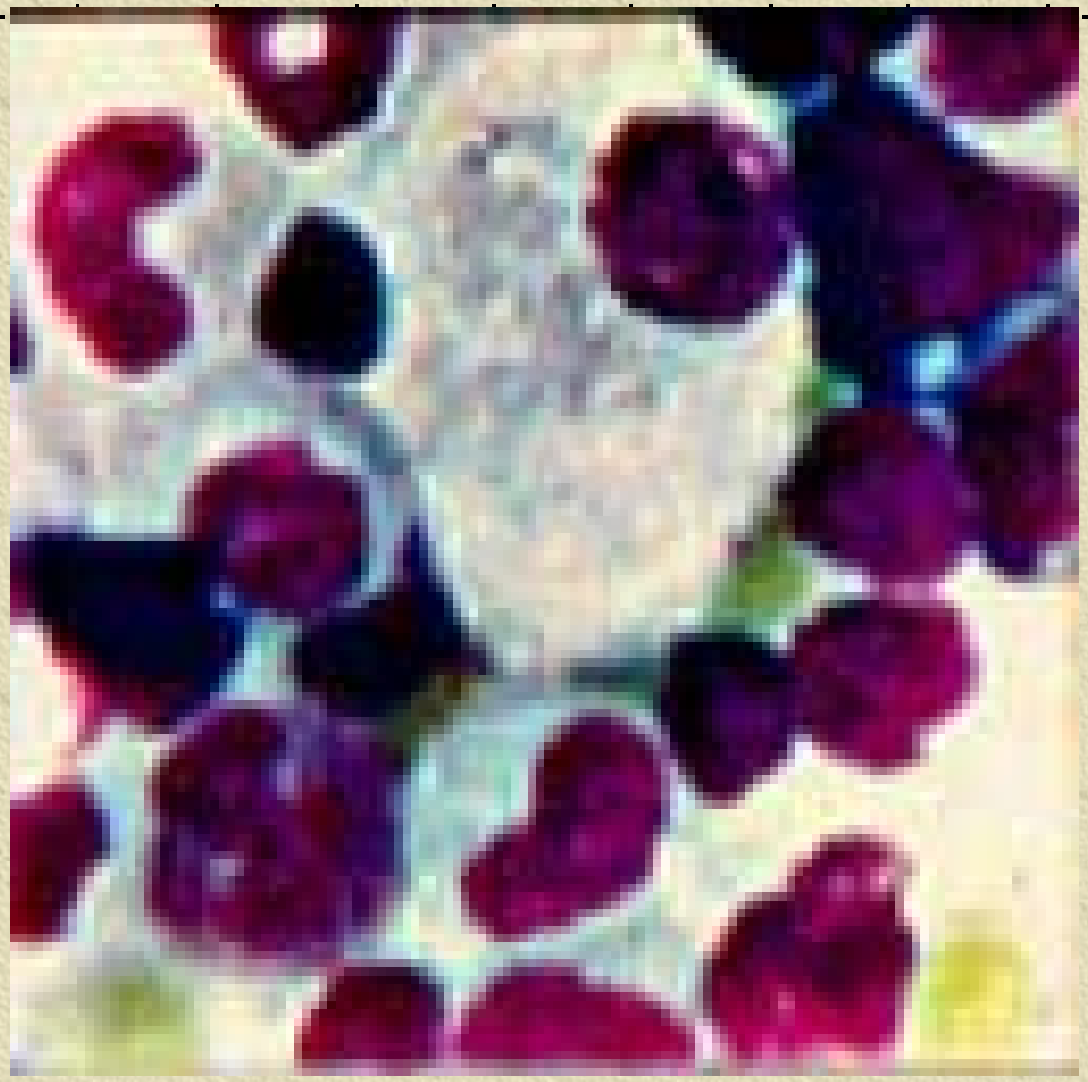
What is Gaucher Disease?

- 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?

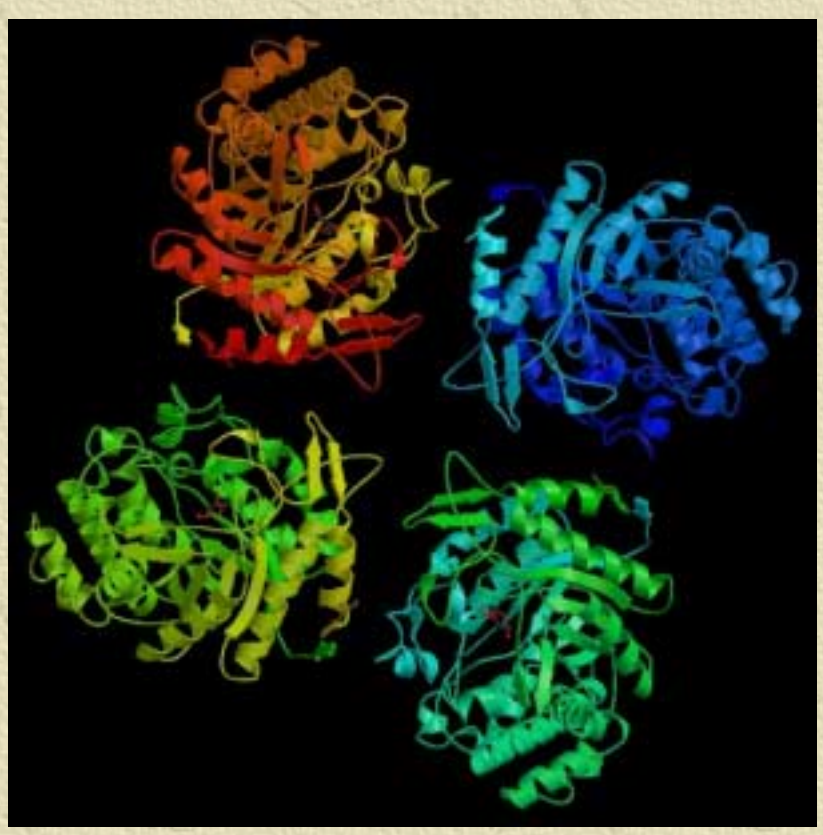
- People with Gaucher disease lack the normal form of the glucocerebrosidase, and are unable to break down glucocerebroside.
- Instead, glucocerebroside remains stored within the lysosomes, preventing the macrophages from functioning normally.
- Enlarged macrophages, due to the accumulated glucocerebroside,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

Gaucher Cell



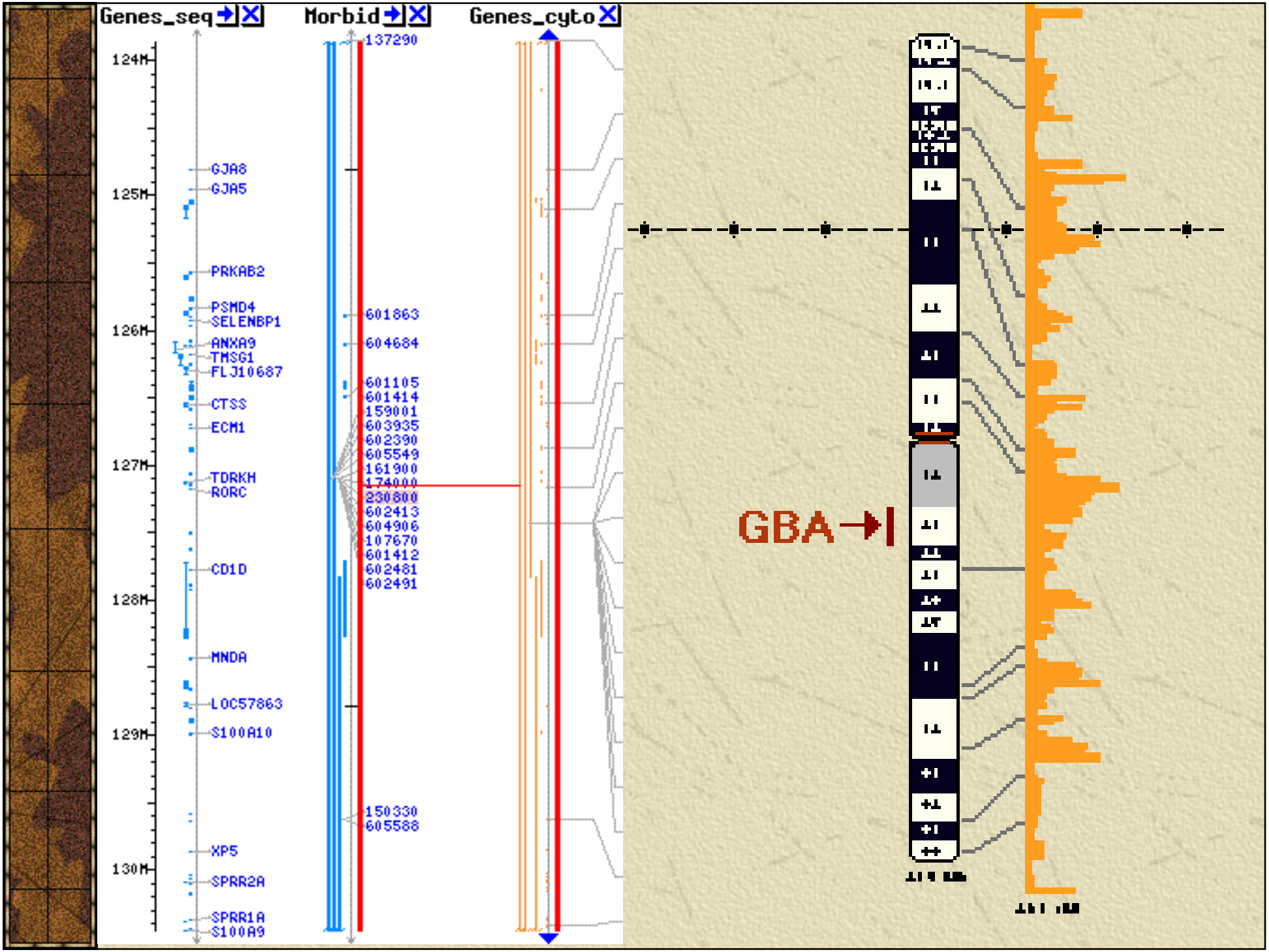
The Enzyme

- 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.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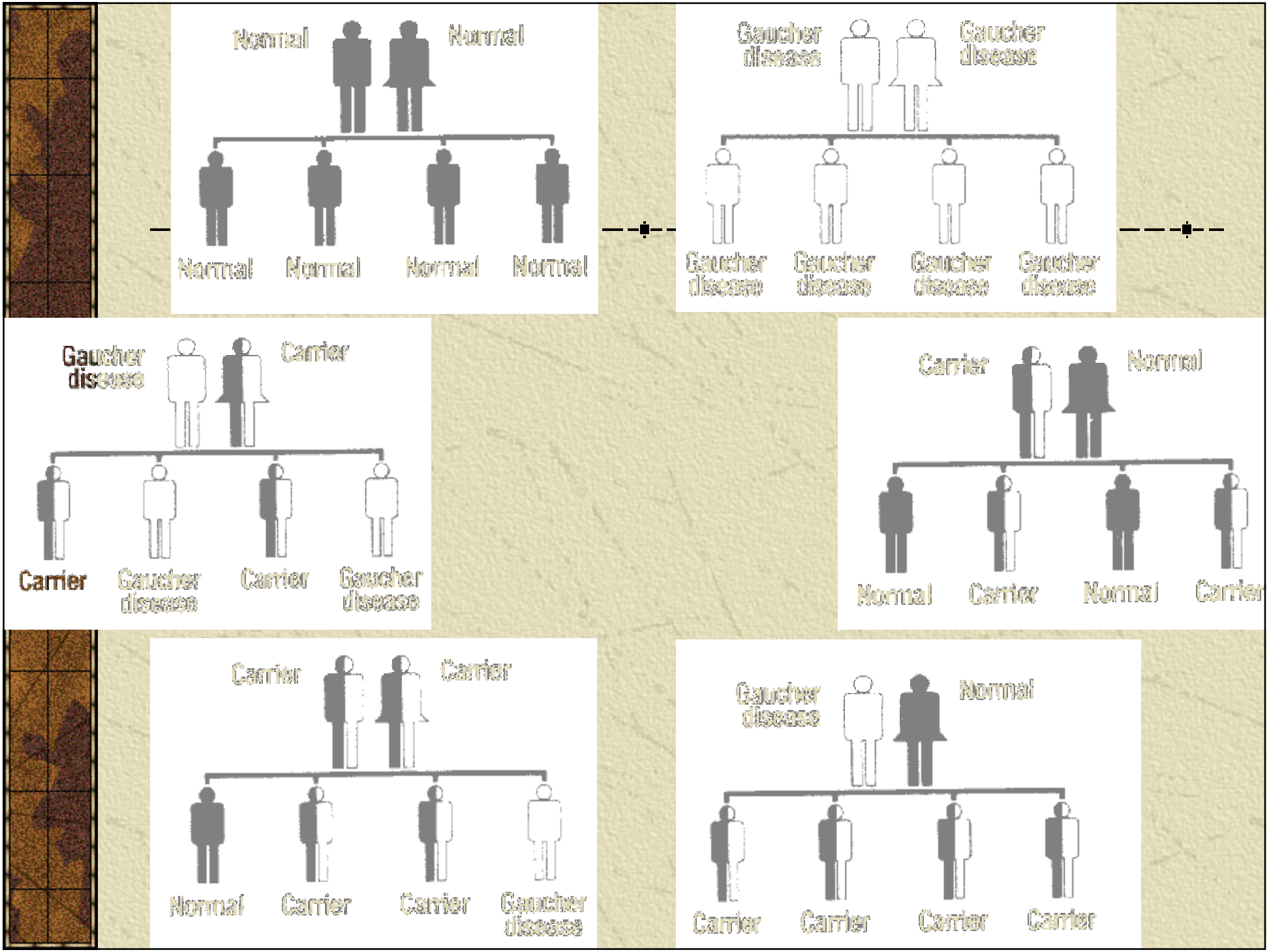
Inheritance Patterns

- 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.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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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