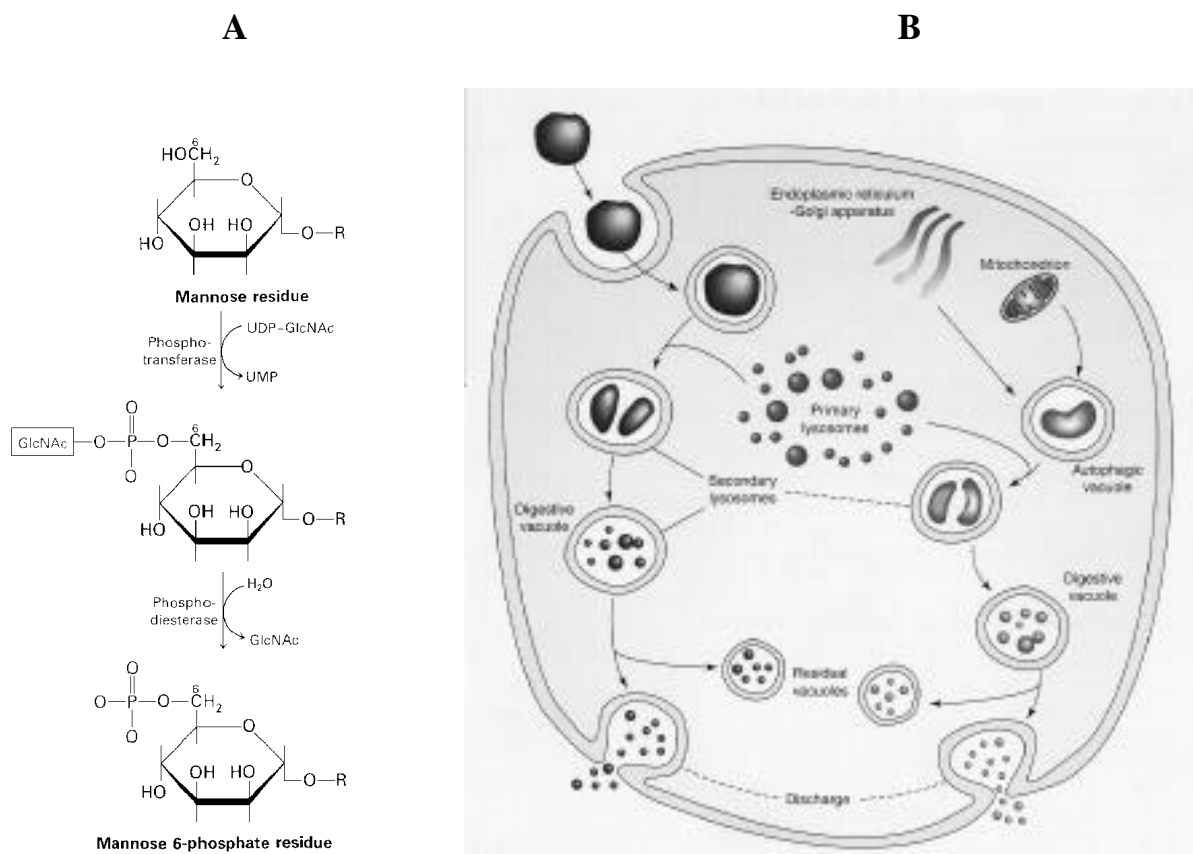# FUNCTION AND CHEMICAL PATHOLOGY OF GAG

Function - Due to their macromolecular and polyanionic nature, proteoglycans can function as a multipurpose "glue" in cellular interactions. They can bind together extracellular matrix components, mediate the binding of cells to the matrix, and capture soluble molecules such as growth factors into the matrix and at the cell surface. They can also serve as a lubricant or as a barrier for microorganisms.
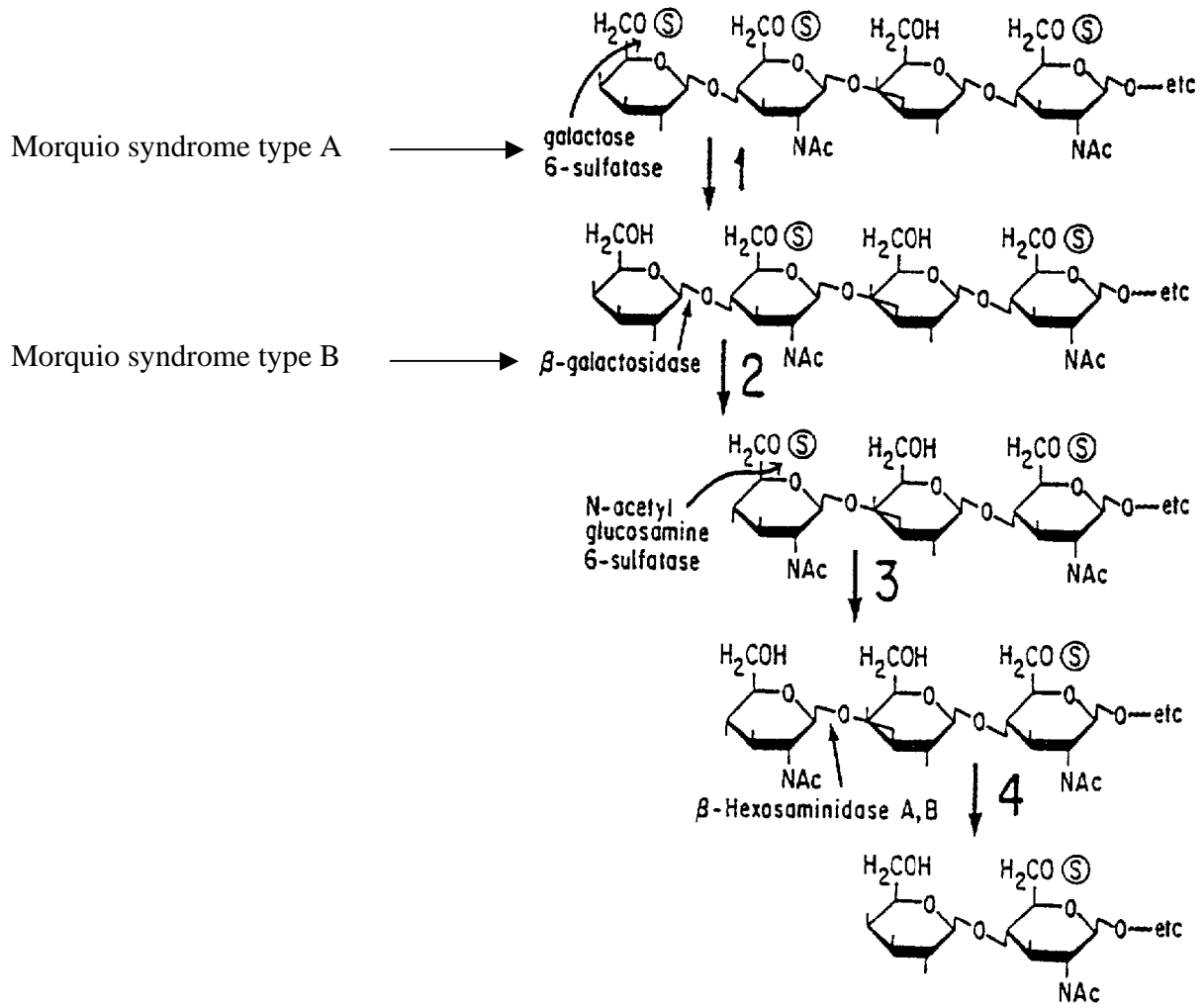
Chemical Pathology - Disorders of glycosaminoglycan metabolism are caused by the deficiency of a particular lysosomal exoglycosidase which is responsible for the catabolism of glycosaminoglycans. Disorders of glycosaminoglycan catabolism are also called *mucopolysaccharidoses* and there are at least 7 types of mucoploysaccharidoses. All mucopolysaccharidoses patients have been found to accumulate glycosaminoglycans (mucopolysaccharides) in various tissues. They also excrete glycosaminoglycans in their urine. *Heparan sulfate*, *dermatan sulfate* and *keratan sulfate* are the three glycosaminoglycans most frequently excreted in the urine or stored in the tissues of patients with mucopolysaccharidoses.

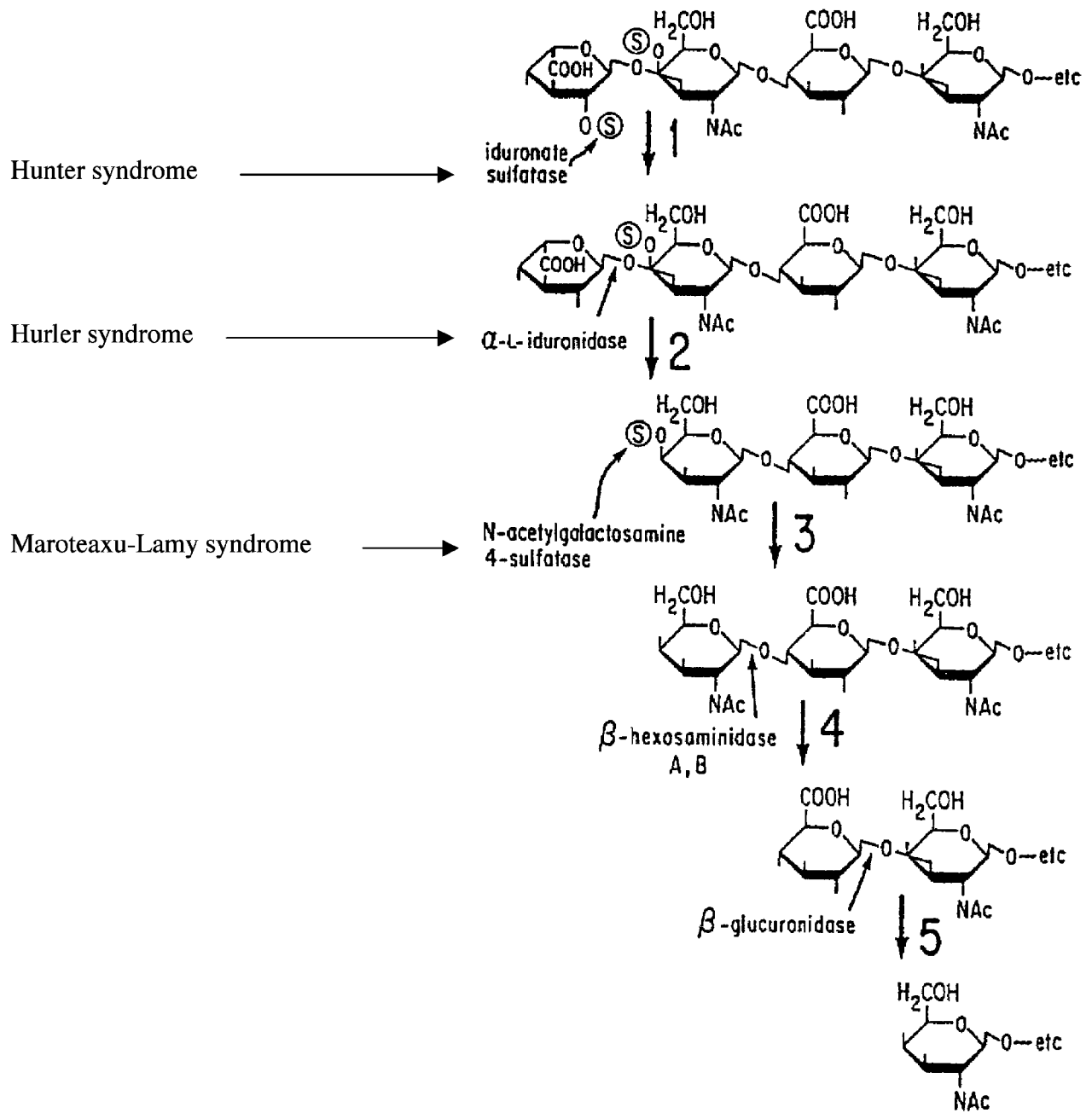## Lysosomal Digestion (See Figure B)

Targeting of Lysosmal Enzymes - Sorting of proteins for their ultimate destinations occurs in conjunction with their glycosylation during passage through the Golgi apparatus. In order to transport enzymes to lysosomes, it is necessary to attach a phosphate to the 6-position of some of the mannoses in the sugar chain of the enzyme. Man-6-P serves as a marker for targeting enzymes to lysosomes. Fig. A shows two-step biosynthesis of Man-6-P residues in lysosomal enzymes. Fig. B shows the schematic representation of lysosomal digestion. **I-Cell disease** arises from the defect in lysosomal enzyme targeting because of a deficiency in the enzyme that transfers GlcNAc-P to the oligosaccharide of the protein.

A   **B**

Stepwise Degradation of Keratan Sulfate

Morquio syndrome type A ⟶ galactose 6-sulfatase

Morquio syndrome type B ⟶ β-galactosidase

N-acetyl glucosamine 6-sulfatase

β-Hexosaminidase A,B

Stepwise Degradation of Dermatan Sulfate

Hunter syndrome $\longrightarrow$ iduronate sulfatase

Hurler syndrome $\longrightarrow$ α-L-iduronidase

Maroteaxu-Lamy syndrome $\longrightarrow$ N-acetylgalactosamine 4-sulfatase

β-hexosaminidase A,B

β-glucuronidase

Stepwise Degradation of Heparan Sulfate