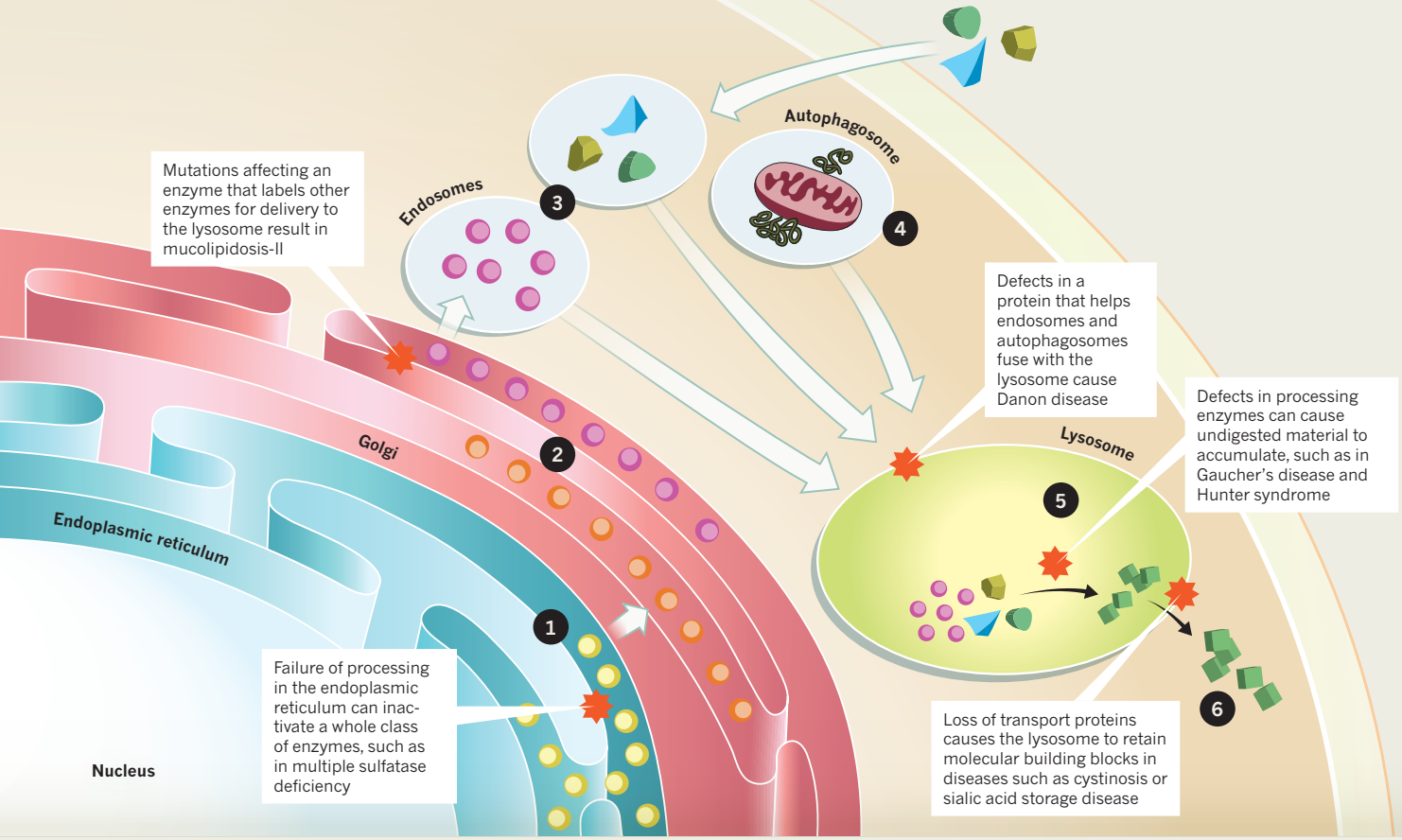
MYRIAD MALADIES



MANY MOVING PARTS

The lysosome uses specialized enzymes to help cells to digest external biological materials and recycle defective proteins and damaged cellular machinery. Many LSDs arise from mutations in the genes that encode those enzymes, but there are numerous other ways in which this process can break down (red stars).

1 The **endoplasmic reticulum** performs the initial processing of newly synthesized lysosomal enzymes

2 The **Golgi apparatus** further processes and labels specific enzymes for delivery to the lysosome

3 **Endosomes** transport enzymes from the Golgi and materials from outside the cell to the lysosome

4 The **autophagosome** delivers damaged organelles and misfolded proteins to the lysosome for recycling

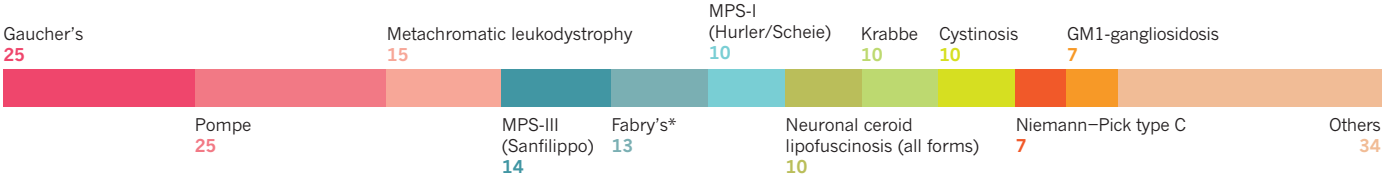
5 Within the **lysosome**, enzymes convert molecules such as sugars, proteins and lipids into simpler building blocks

6 Molecular building blocks are released into cell for reuse

COLLECTIVELY COMMON, INDIVIDUALLY RARE

LSDs are not especially rare; estimates suggest that 1 in just over 5,000 newborns will be affected. However, each individual disease occurs with much lower frequency — the most common, Gaucher's disease, affects only 1 in 40,000 newborns worldwide, and the rarest have been described only a handful of times. The diseases shown are those for which there are most data. Numbers have been estimated and are approximate.

180 PER 1 MILLION LIVE BIRTHS



Others: Mucopolysaccharidosis (MPS)-IV, 5.0; MPS-VII, 4.0; Niemann–Pick type A/B, 4.0; MPS-II (Hunter)*, 3.8; Sandhoff, 3.2; Wolman, 2.9; Tay–Sachs, 2.9; MPS-VI, 2.5; alpha-mannosidosis, 2.0; pycnodysostosis, 1.3; Danon, 0.3; Schindler, 0.3; beta-mannosidosis, 0.3; fucosidosis, 0.3; aspartylglucosaminuria, 0.3; Farber, 0.3; multiple sulfatase deficiency, 0.3; galactosialidosis, 0.3; sialic acid storage, 0.3.

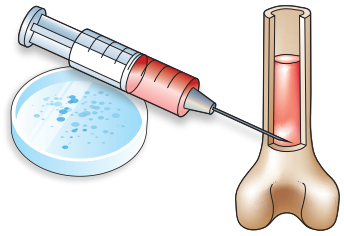
*Almost exclusively in males.

SOURCES: US NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE; GENETICS HOME REFERENCE/NATIONAL LIBRARY OF MEDICINE; WWW.OMIM.ORG; WWW.ORPHA.NET; GENE REVIEWS; MEDSCAPE

Lysosomal storage disorders (LSDs) highlight the diverse ways in which the failure of a single organelle can bring cells to their knees. Most are rare and poorly understood, making the development of therapies a daunting task. By ***Michael Eisenstein****, infographic by* ***Denis Mallet****.*

BONE-MARROW TRANSPLANT

This is an aggressive treatment in which the patient's blood-cell-producing haematopoietic stem cells are wiped out by chemotherapy and replaced with healthy donor cells.



POTENTIAL ROADS TO RECOVERY

The past 25 years have seen considerable progress in the development of treatments that can improve the quality of life for some patients. Most treatments focus on changing intracellular processes. The exception is bone-marrow transplant, in which the patient receives an entire set of healthy stem cells from a suitable donor.

① **Enzyme-replacement therapy** involves replacing missing or defective enzymes with synthetic counterparts, which are internalized by cells and delivered to lysosomes

② **Substrate-reduction therapy** blocks the production of materials that would otherwise accumulate in the lysosome owing to a lack of appropriate digestive enzymes

③ **Chaperone therapy** protects or refolds mutant enzymes. This prevents them from being degraded in the endoplasmic reticulum and ejected, and allows them to reach the lysosome.

④ In **gene therapy**, a functional replacement enzyme-producing gene is delivered using a vector such as a virus. This technology is still being developed (page S158).

THE LONG ROAD TO DISCOVERY

The first LSDs were identified more than 80 years before researchers were able to identify the cellular structures involved. Since then, new LSDs have been identified along with, more recently, the genes involved and drugs that help to repair the damage.