Given the substantial morbidity and health care costs associated with surgical-site infection, we need more innovative trials testing novel approaches to further lower the infection risk. Moreover, a deeper understanding of the individual patient's microbiome may allow for tailored interventions to further decrease the incidence of infection. Lister was able to make a quantum leap to markedly reduce the risk of infection and to lower mortality. We await next-generation innovations to achieve zero surgical-site infections.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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SCIENCE BEHIND THE STUDY
Elizabeth G. Phimister, Ph.D., *Editor*

N-Acetyl-L-Leucine and Neurodegenerative Disease

Cynthia J. Tifft, M.D., Ph.D.

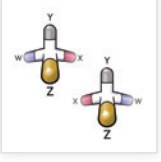
Lysosomal storage disorders, although individually rare, have a collective incidence of 1 in 5000 live births. Moreover, 70% of the nearly 70 known lysosomal storage disorders affect the central nervous system.[1] These monogenic disorders cause perturbation in lysosome function (see Key Concepts), leading to metabolic instability, dysregulation of mammalian target of rapamycin (mTOR; normally, mTOR suppresses inflammation), impaired autophagy, and neuronal cell death.[2] Several therapies that address the underlying pathologic processes of lysosomal storage disorders are approved or under development; these include enzyme-replacement therapy, substrate-reduction therapy, molecular chaperone therapy, gene therapy, gene editing, and neuroprotective therapies (Fig. 1).

Niemann–Pick disease type C is a lysosomal storage disorder of cellular cholesterol trafficking caused by biallelic mutations in *NPC1* (occurring in 95% of patients with the disorder) or *NPC2* (occurring in 5%). The phenotypic spectrum of Niemann–Pick disease type C spans rapid, fatal

Key Concepts

Lysosome

An acidic intracellular organelle, bound by a phospholipid bilayer membrane, that has key functions in cellular homeostasis, including the breakdown and recycling of macromolecules (carbohydrates, lipids, nucleic acids, and proteins), control of nutrient sensing, and calcium signaling. Lysosomes can fuse with endosomes, phagosomes, and autophagosomes and, by fusing with the plasma (cell) membrane, facilitate cell–cell communication.



Enantiomer

One of a pair of molecules, each of which is the mirror image of the other. They cannot, therefore, be superimposed on one another. A racemate is a mixture of the two enantiomers. Biologic molecules may naturally occur in one enantiomeric form that has different properties from its opposing enantiomer. Understanding the properties and effects of each enantiomer is therefore important in pharmacology.

An expanded illustrated glossary is available at NEJM.org

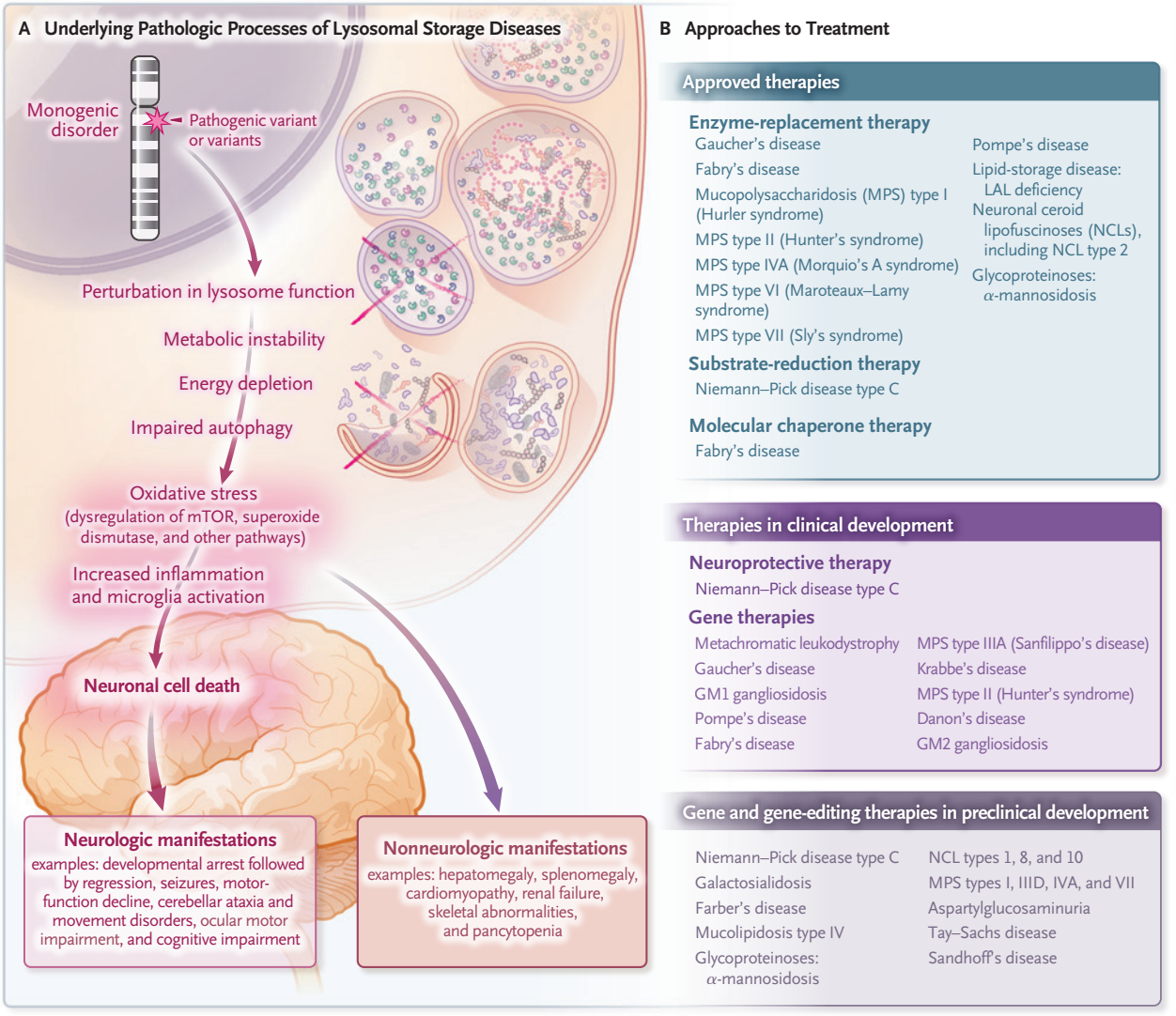


Figure 1. Approaches to Treatment of Lysosomal Storage Diseases.

Bremova-Ertl et al.[3] describe a new approach to the treatment of lysosomal storage diseases that uses a modified amino acid, *N*-acetyl-L-leucine, as an agent to improve the neurologic function and symptoms in patients with Niemann–Pick disease type C. The neuroprotective potential is currently being evaluated in the extension phase of the reported randomized clinical trial. Approved therapies for lysosomal storage disorders include enzyme-replacement therapy, substrate-reduction therapy, and molecular chaperone therapy. Another approach, gene therapy, is under clinical development for several disorders, and gene and gene-editing therapies are in preclinical development. LAL denotes lysosomal acid lipase, and mTOR mammalian target of rapamycin.

neurologic regression in infancy to late-infantile, juvenile, and adult-onset forms characterized by splenomegaly, supranuclear gaze palsy, and neurologic features such as cerebellar ataxia, dysarthria, and progressive dementia.[4]

In this issue of the *Journal*, Bremova-Ertl et al.[3] report the results of a double-blind, placebo-controlled, crossover trial of a potentially neuroprotective agent, the amino acid analogue *N*-acetyl-L-leucine (NALL) to treat Niemann–Pick disease type C. They enrolled 60 symptomatic juvenile and adult patients and found a significant improvement in the total score on the Scale for the Assessment and Rating of Ataxia (primary end point).

Clinical trials of *N*-acetyl-DL-leucine (Tanganil),

a racemate of NALL and *N*-acetyl-D-leucine, appear to be largely empirically driven: its mechanism of action has not been definitively elucidated. *N*-acetyl-DL-leucine has been approved since the 1950s for the treatment of acute vertigo; in that context, it was thought to act by rebalancing hyperpolarized and depolarized medial vestibular neurons, as shown in animal models.[5] Subsequently, Strupp et al. reported a short study in which they observed symptomatic improvement in 13 patients with degenerative cerebellar ataxias of differing causes, findings that ignited interest in repurposing the drug.[6]

AND THE MECHANISM?

The mechanism through which *N*-acetyl-DL-leucine brings about improvement of neurologic function is not delineated, although studies of two mouse models, one of Niemann–Pick disease type C[7] and another of Sandhoff's disease (another neurodegenerative lysosomal disorder),[8] have provided insight and focused attention on NALL. Specifically, increased survival in *Npc1*$^{-/-}$ mice treated with *N*-acetyl-DL-leucine or NALL (the L-enantiomer), but not in those treated with *N*-acetyl-D-leucine (the D-enantiomer), identified NALL as the active form of the drug.[7] In a similar study of a mouse model (*Hexb*$^{-/-}$) of Sandhoff's disease, *N*-acetyl-DL-leucine produced a modest but significant increase in lifespan.[8]

To explore the mechanism of action of *N*-acetyl-DL-leucine, pathways that are involved in leucine metabolism were interrogated by measurement of metabolites in cerebellar tissues from animals with the mutation. In the model of Sandhoff's disease, *N*-acetyl-DL-leucine normalized glucose and glutamate metabolism, increased autophagy, and increased levels of superoxide dismutase, a scavenger of reactive oxygen species.[8] In the model of Niemann–Pick disease type C, altered glucose and antioxidant metabolism and improvements in mitochondrial energy metabolism were observed.[7] Although L-leucine is a potent activator of mTOR, no changes in the levels or phosphorylation of mTOR were noted after treatment with *N*-acetyl-DL-leucine or its enantiomers in either mouse model.

Neuroprotective effects of NALL were observed with the use of a mouse model of cortical impact–induced traumatic brain injury.[9] These included a decrease in neuroinflammatory markers, attenuation of cortical cell death, and improvement in autophagy flux. The injured mice showed recovery of motor and cognitive function and a reduction in lesion volume after NALL treatment.

WHAT'S NEXT?

Neuroinflammation in the central nervous system is a hallmark in the pathogenesis of most neurodegenerative lysosomal storage disorders. If neuroinflammation is attenuated by treatment with NALL,[9] clinical improvement may be seen in many and perhaps all neurodegenerative lysosomal storage disorders. As shown in the current study, synergy with other therapies for lysosomal storage disorders would be anticipated.

Many lysosomal storage disorders also feature cerebellar ataxia. A decrease in ataxia and improvement in fine motor coordination after NALL treatment have been reported in an international study involving children and adults with GM2 gangliosidosis (Tay–Sachs disease and Sandhoff's disease).[10] However, a large, multicenter, double-blind, randomized, placebo-controlled trial involving patients with cerebellar ataxia of mixed (hereditary, nonhereditary, and unknown) cause did not show a clinically significant difference associated with *N*-acetyl-DL-leucine treatment.[11] This finding suggests that trials involving persons with only heritable cerebellar ataxias may be needed to show efficacy and perhaps provide clues about the mechanism of action. In addition, to the extent that NALL attenuates neuroinflammation and neuroinflammation contributes to outcomes in traumatic brain injury, trials of NALL to treat traumatic brain injury should be considered.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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