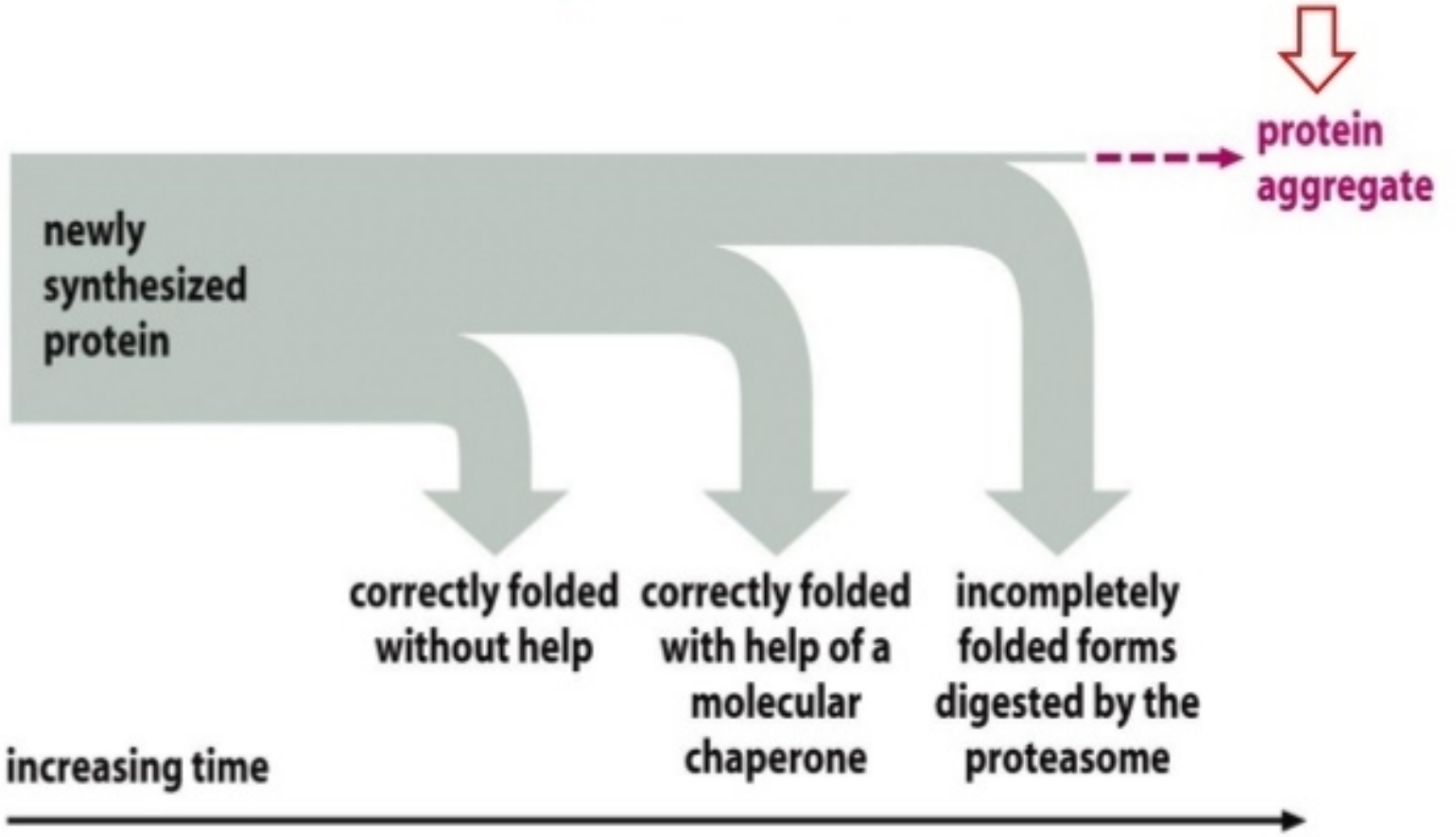
Defects in Protein folding

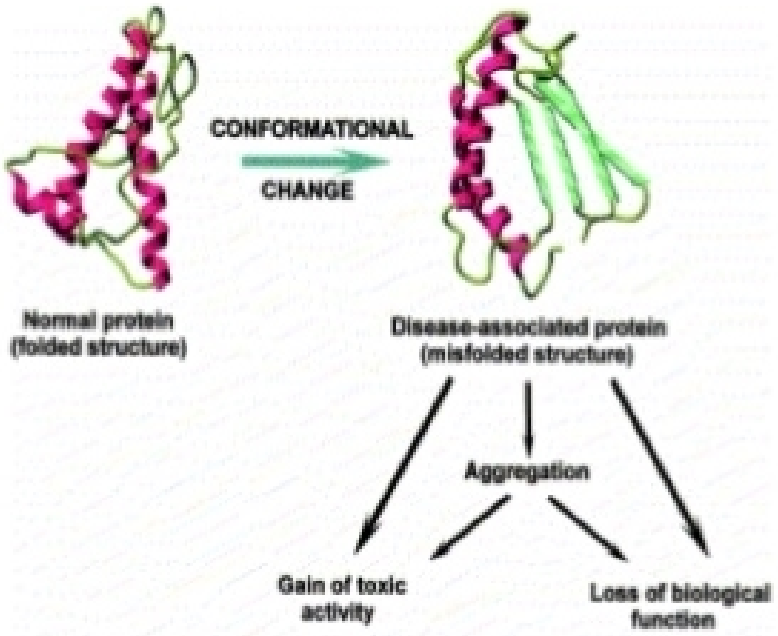
Potential fates of newly-synthesized proteins



Source: Molecular biology of the cell (Garland Science 2008)

Protein Misfolding Diseases (PMDs)

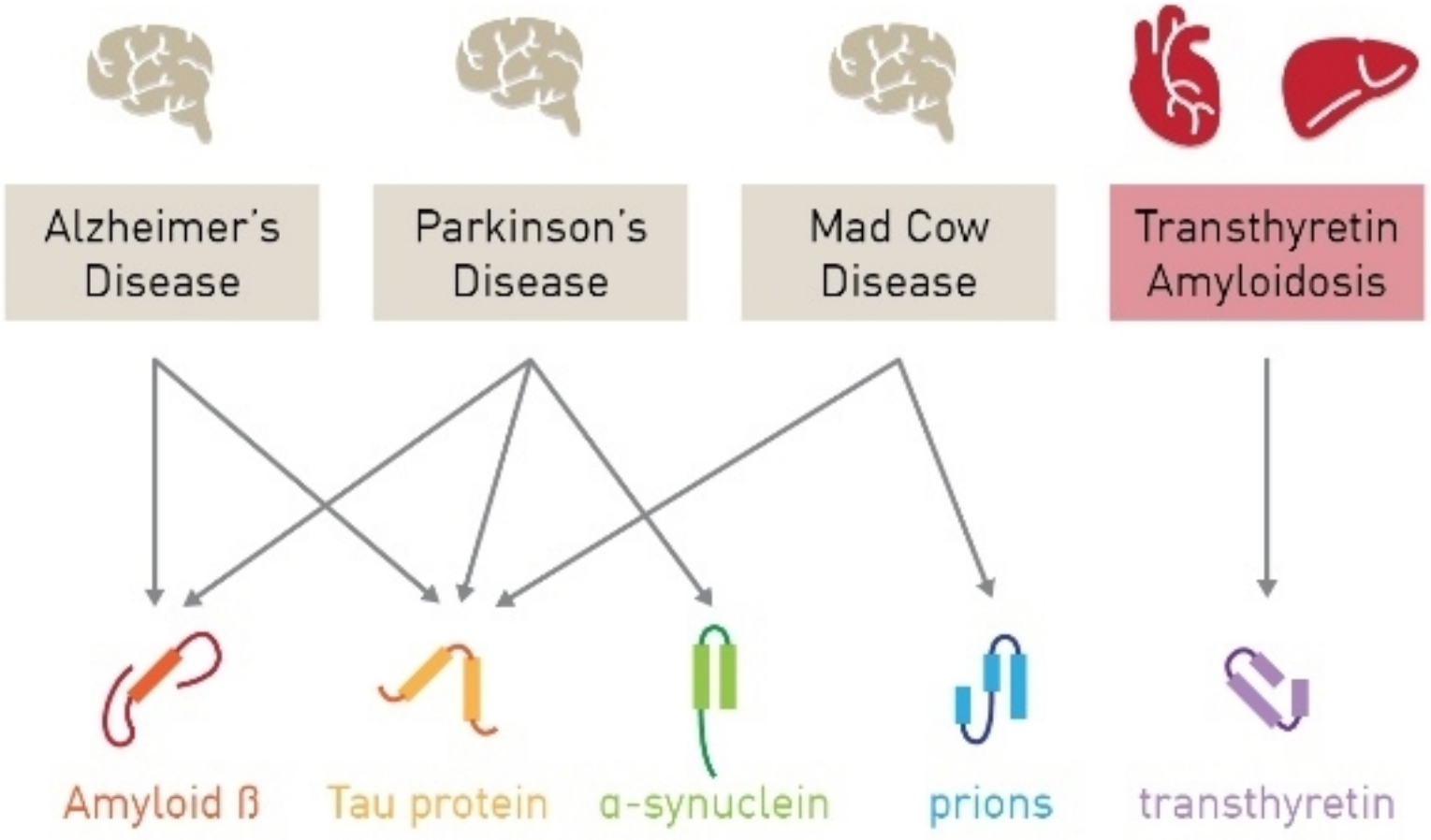
* Many inherited diseases result from mutant proteins that evade quality control processes, fold abnormally and ultimately form aggregates.
* The gradual decline of protein quality controls with age can also lead to disease by permitting normal proteins to form aggregates that can impair cellular functions.
* Many neurodegenerative diseases, including Huntington's and Alzheimer's, are associated with the presence of misfolded protein aggregates in neuronal tissue.
* The aggregates in patients can be intracellular (nuclear and/or cytoplasmic) or extracellular.

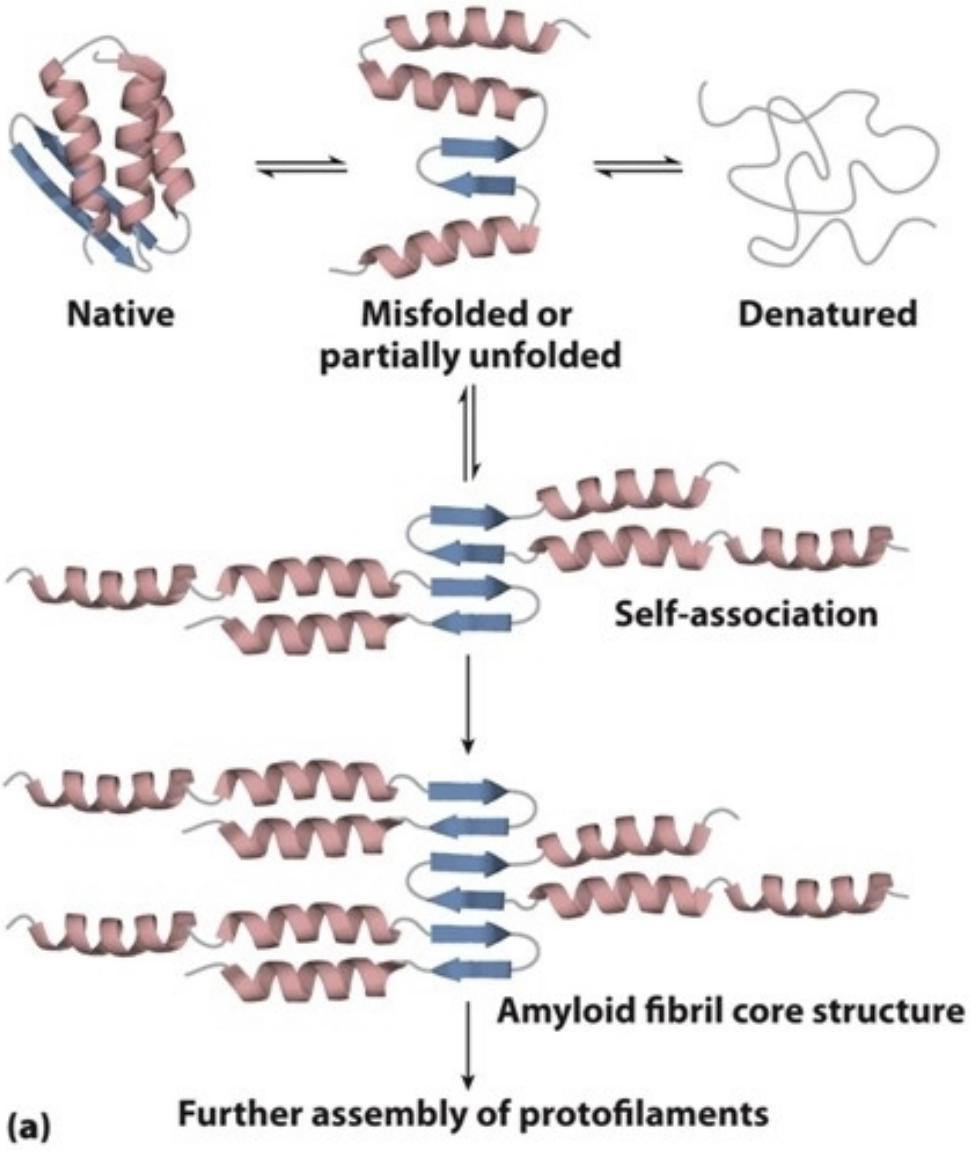


Proteins involved in human diseases caused by amyloid formation

Proteinopathy	Aggregating protein(s)
Alzheimer's disease	*Amyloid beta (Ab) peptide; Tau*
Parkinson's disease	*a-synuclein*
Multiple tauopathies	*Tau protein (microtubule associated)*
Huntington's disease	*Huntingtin with tandem glutamine repeats*
Amyotrophic lateral sclerosis	*Superoxide dismutase 1*
Spongiform encephalopathies	**Prion proteins (toxic)**
Familial amyloidotic polyneuropathy	*Transthyretin (mutant forms)*

Misfolded proteins diseases





Formation of disease-causing amyloid fibrils

Please refer page no. 149, figure 4-32, Lehninger 6th edition

Lehninger Principles of Biochemistry, Sixth Edition
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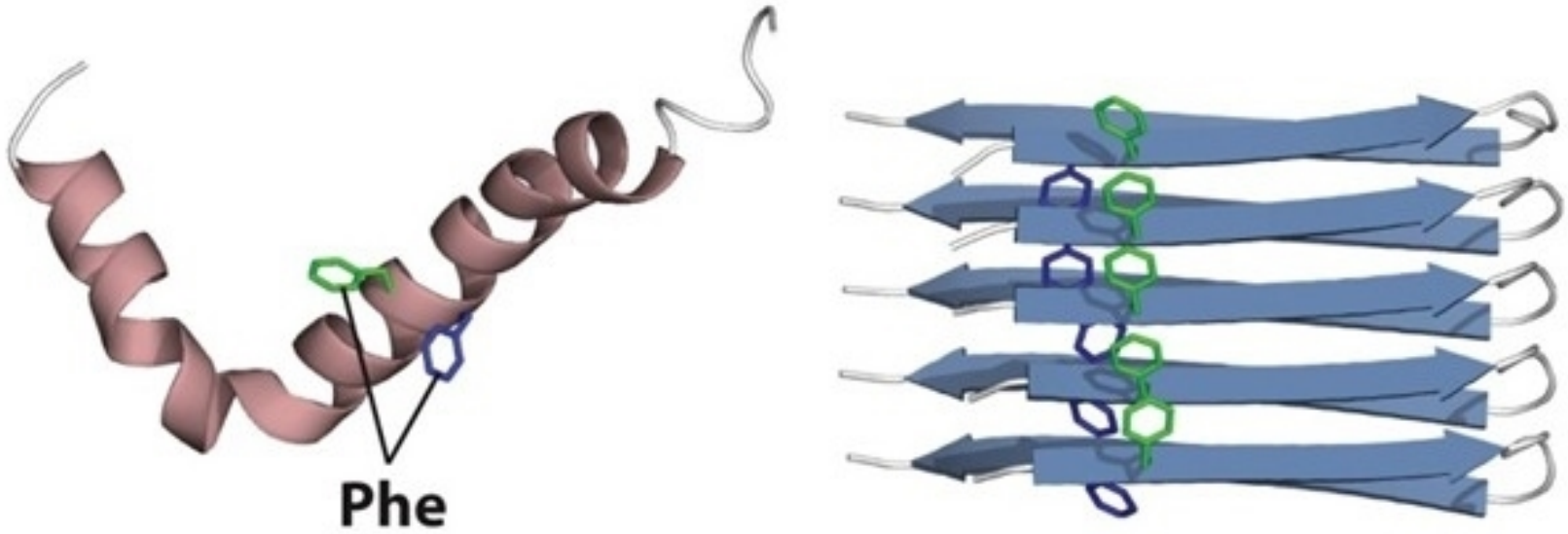

Figure 4-32

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Mechanism of protein misfolding in eukaryotes

Stress/Protein synthesis > Protein folding capacity of Endoplasmic Reticulum

Results in the activation of Unfolded Protein Response **(UPR)**

Increases concentration of Chaperons/ decrease the rate of overall protein synthesis

Formation of amyloid aggregates

a. Degraded by autophagy
b. Degraded by proteases through Ubiquitin-proteosome system

Note: Defects in any of the above mentioned systems decrease the capacity to deal with misfolded proteins

Systemic Amyloidosis

Amyloidosis that affects tissues throughout the body is referred to as **Systemic amyloidosis**. It can cause serious changes throughout the body. It is classified into Primary Systemic Amyloidosis and Secondary Systemic Amyloidosis

Primary Systemic Amyloidosis

a. It is caused by deposition of fibrils consisting of misfolded immunoglobulin light chains or fragments of light chains derived from proteolytic degradation.
b. It is also called AL amyloidosis
c. The mean age of onset is about 65 years
d. Symptoms include: fatique, horseness, swelling, weight loss and death within first year after diagnosis
e. It usually affects the heart, kidneys, liver and nerves

Secondary Systemic Amyloidosis

a. It is also called AA amyloidosis
b. It is usually triggered by an inflammatory disease such as rhematoid arthritis, tuberculosis, cystic fibrosis and some cancers
c. It is characterised by a sharp increase in secretion of an amyloid-prone polypeptide called serum amyloid A (SAA)
d. It most commonly affects the liver, kidneys, spleen and heart.
e. It is generally fetal within few years of its onset
f. Mutations in transthyretin is an example of secondary systemic amyloidosis as a variety of mutations of this protein lead to amyloid deposition concentrated around different tissues, thus producing different symptoms.

Amyloidosis of particular organ

In some cases amyloid-prone protein is secreted by affected tissue and its locally high concentration leads to amyloid deposition around that tissue.

❖ For example; secretion of amyloid polypeptide (IAPP) or amylin by β cells of islet of langerhans of pancreas leads to amyloid deposits around the islets and gradually destroys these cells. This ultimately results in **type-2 diabetes mellitus**

❖ **Neurodegenerative disorders:** Accumulation of amyloid-like aggregates is a hallmark of numerous neurodegenerative disorders. Some examples are mentioned in next slide

a. **Alzeimer's disease:** It results due to the extracellular deposition of amyloid-β peptide by neurons. (plz refer slide no. 7, figure 4-32).
b. **Parkinsonism:** It results due to inherited mutations in the *tau* protein inside the neurons. This mutation results in frontotemporal dementia and parkinsonism (a condition with symptoms resembling parkinson disease)
c. **Parkinson Disease:** It results due to aggregation of misfolded protein α-synuclein. This aggregates into spherical filamentous masses called Lewy bodies.
d. **Huntington disease:** It results due to intracellular aggregation of huntingtin protein which has a long polyglutamine repeat.

Other Protein misfolding disease

1. Cystic Fibrosis: It results due to mutation in CFTR protein which acts as a chloride channel. CFTR stands for **cystic fibrosis transmembrane conductance regulator.** The mutation responsible for cystic fibrosis in 70 % of cases results in deletion of a phenylalanine residue at position 508.

The mutant protein folds incorrectly which interferes with its insertion in the plasma membrane, resulting in reduced chloride ion and water movement across the plasma membranes in epithelial cells that line the airways, the digestive tract and exocrine glands (pancreas, sweat glands, bile ducts and vas deferens)

Diminished export of chloride ions is accompanied by diminished export of water from cells, causing mucus on the surfaces of the cells to become dehydrated, thick, and sticky. This reduces the ability of cilia to sweep away bacteria and increases the probability of infection causing progressive damage to the lungs and reduced respiratory efficiency

2. Prion diseases are a group of neurodegenerative disorders that can affect both humans and animals

They are caused by the deposition of abnormally folded proteins in the brain, particularly the misfolded of proteins called prion proteins (PrP). Misfolded PrP begins to accumulate and forms clumps within the brain, damaging and killing nerve cells.

This damage results in the formation of tiny holes in brain tissue, making it appear sponge-like under a microscope. This is the reason that prion diseases refeerred to as "Spongiform Encephalopathies" (plz refer box 4-6, page no. 150-151, Lehninger 6^{th} edition)

Prion disease could be acquired (exposure to abnormal PrP from an outside source; Inherited (mutations present in the gene that codes for PrP) or sporadic (misfolded PrP may develop for some unknown reason)

Some examples of prion disease are: Bovine spongiform encephalopathy (mad cow disease), Kuru, Creutzfeldt-Jacob disease in humans, scrapie in sheep, chronic wasting disease in deer and elk.