tissues become grossly visible, they are termed **xanthomas** (Fig. 1-23B).

Abnormal Proteins

Numerous acquired and inherited diseases are characterized by the intracellular accumulation of abnormal proteins. The deviant tertiary structure of the protein may result from an inherited mutation that alters the normal primary amino acid sequence or may reflect an acquired defect in protein folding. The following are examples:

- **α_1-Antitrypsin deficiency** is a heritable disorder in which mutations in the coding gene for α_1-antitrypsin yield an insoluble protein that is not easily exported. It accumulates in liver cells (Fig. 1-23C), causing cell injury and cirrhosis (see Chapter 14).
- **Prion diseases** comprise a group of neurodegenerative disorders (spongiform encephalopathies) caused by the accumulation of abnormally folded prion proteins. The anomaly reflects the conversion of the normal α-helical structure to a β-pleated sheet. Abnormal prion proteins may result from an inherited mutation or from exposure to the aberrant form of the protein (see Chapter 28). The function of normal prion protein is not yet clear. It has been reported to have SOD-like antioxidant activity, a role in T-lymphocyte–dendritic cell interactions, the ability to enhance neural progenitor proliferation and a key role in development of long- term memory.
- **Lewy bodies** (α-synuclein) are seen in neurons of the substantia nigra in Parkinson disease (Chapter 28).
- **Neurofibrillary tangles** (tau protein) characterize cortical neurons in Alzheimer disease (Chapter 28).
- **Mallory bodies** (intermediate filaments) are hepatocellular inclusions in alcoholic liver injury (Chapter 14).

MOLECULAR PATHOGENESIS: Translation of mRNA by ribosomes produces a linear chain of amino acids that lacks a defined three-dimensional structure. In order to perform its specific function, each protein must be folded into its own native three-dimensional conformation. Curiously, it is energetically more favorable for the cell to produce many foldings and then edit the protein repertoire than to produce only a single functional conformation. Molecular chaperones associate with polypeptides in the endoplasmic reticulum and promote correct folding, after which they dissociate from those proteins that have assumed the correct conformation (Fig. 1-24). Protein synthesis presents a number of possible outcomes:

- The primary sequence is correct and proper folding into the appropriate functional conformation occurs.
- The primary sequence may be correct, but the protein does not fold correctly, as indicated above, owing to the random energetic fluctuations.
- A mutated protein (i.e., one with an incorrect amino acid sequence) does not fold correctly.
- A conformationally correct protein may become unfolded or misfolded due to an unfavorable environment (e.g., altered pH, high ionic strength, oxidation, etc.).

Protein misfolding is an intrinsic tendency of proteins and occurs continuously. The misfolded protein load is eliminated by protein quality control systems, including the ubiquitin–proteasome system and autophagic pathways. Evolutionary preference for energy conservation has dictated that a substantial proportion of newly formed proteins are rogues unsuitable for the society of civilized cells.

The protein quality control system may fail because of a malfunction of protein quality control or overload of this system. In either case, misfolded proteins accumulate in the cell as amorphous aggregates or as fibrils. They may lead to cell injury, reflecting either a decrease in a necessary activity **(loss of function)** or a harmful increase in a cellular enterprise that alters a delicate balance of forces within the cell **(gain of function).**

Numerous hereditary and acquired diseases are caused by evasion of the quality control system designed to promote correct folding and eliminate faulty proteins. Misfolded proteins can injure the cell in a number of ways:

- **Loss of function:** Certain mutations prevent correct folding of crucial proteins, which then do not function properly or cannot be incorporated into the correct site. For example, some mutations that lead to cystic fibrosis cause misfolding of an ion channel protein, which is then degraded. Failure of the protein to reach its destination at the cell membrane results in a defect in chloride transport that produces the disease cystic fibrosis. Other examples of loss of function include mutations of the low-density lipoprotein (LDL) receptor in certain types of hypercholesterolemia and mutations of a copper transport ATPase in Wilson disease.
- **Formation of toxic protein aggregates:** Defects in protein structure may be acquired as well as genetic. Thus, particularly in nondividing cells, age-related impairment of cellular antioxidant defenses leads to protein oxidation, which commonly alters protein tertiary structure, exposing interior hydrophobic amino acids that are normally hidden. In situations of mild to moderate oxidative stress, 20S proteasomes recognize the exposed hydrophobic moieties and degrade these proteins. However, if oxidative stress is severe, these proteins aggregate by virtue of a combination of hydrophobic and ionic bonds. Such aggregates are insoluble and tend to sequester Fe^{2+} ions, which in turn help generate additional ROS (see above), after which aggregate size increases. Whether or not the proteins contained in the aggregates are ubiquitinated, the aggregates are indigestible (Fig. 1-25). Any Ub bound to them is lost, which may cause a cellular deficit in Ub and impair protein degradation in general. Both by virtue of their generation of toxic ROS and their inhibition of proteasomal degradation, these aggregates may lead to cell death. Accumulation of amyloid β protein in Alzheimer disease and α-synuclein in Parkinson disease may occur by this type of mechanism.
- **Retention of secretory proteins:** Many proteins that are destined to be secreted from the cell require a correctly folded conformation to be transported through cellular compartments and released at the cell membrane. Mutations in genes that encode such proteins (e.g., α_1-antitrypsin) eventuate in cell injury because of massive accumulation of misfolded proteins within the liver cell. Failure to secrete this antiprotease into the circulation