Collagens and connective tissue diseases

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Lecture 46

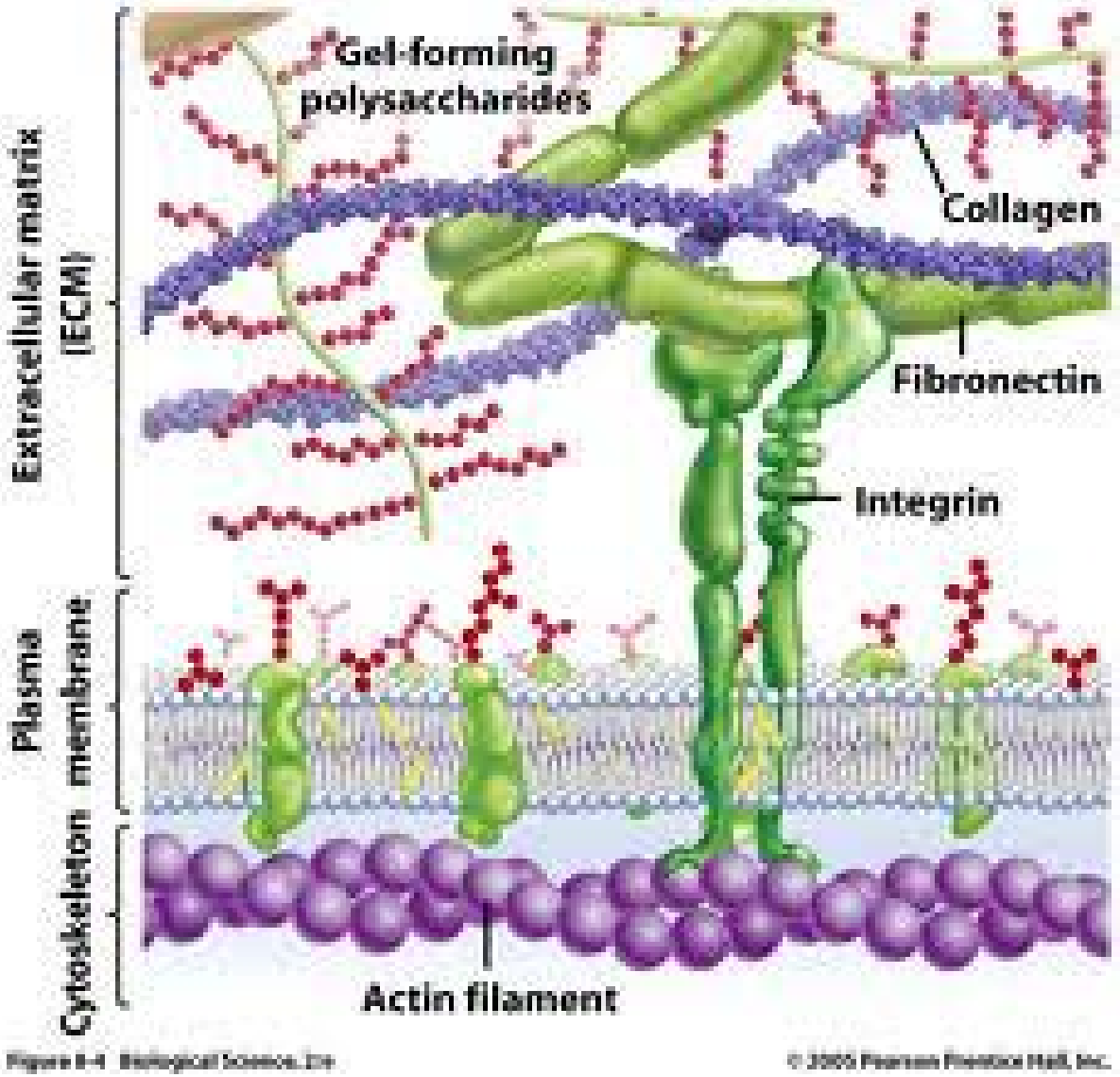
~~**May 16, 2014**~~

Fibrous proteins—collagens and elastin

- Insoluble
- Stable
- Long biological half-life
- High tensile strength and contractibility, respectively

Each fibrous protein exhibits special mechanical properties resulting from their unique structures

These proteins function in the extracellular matrix (ECM)



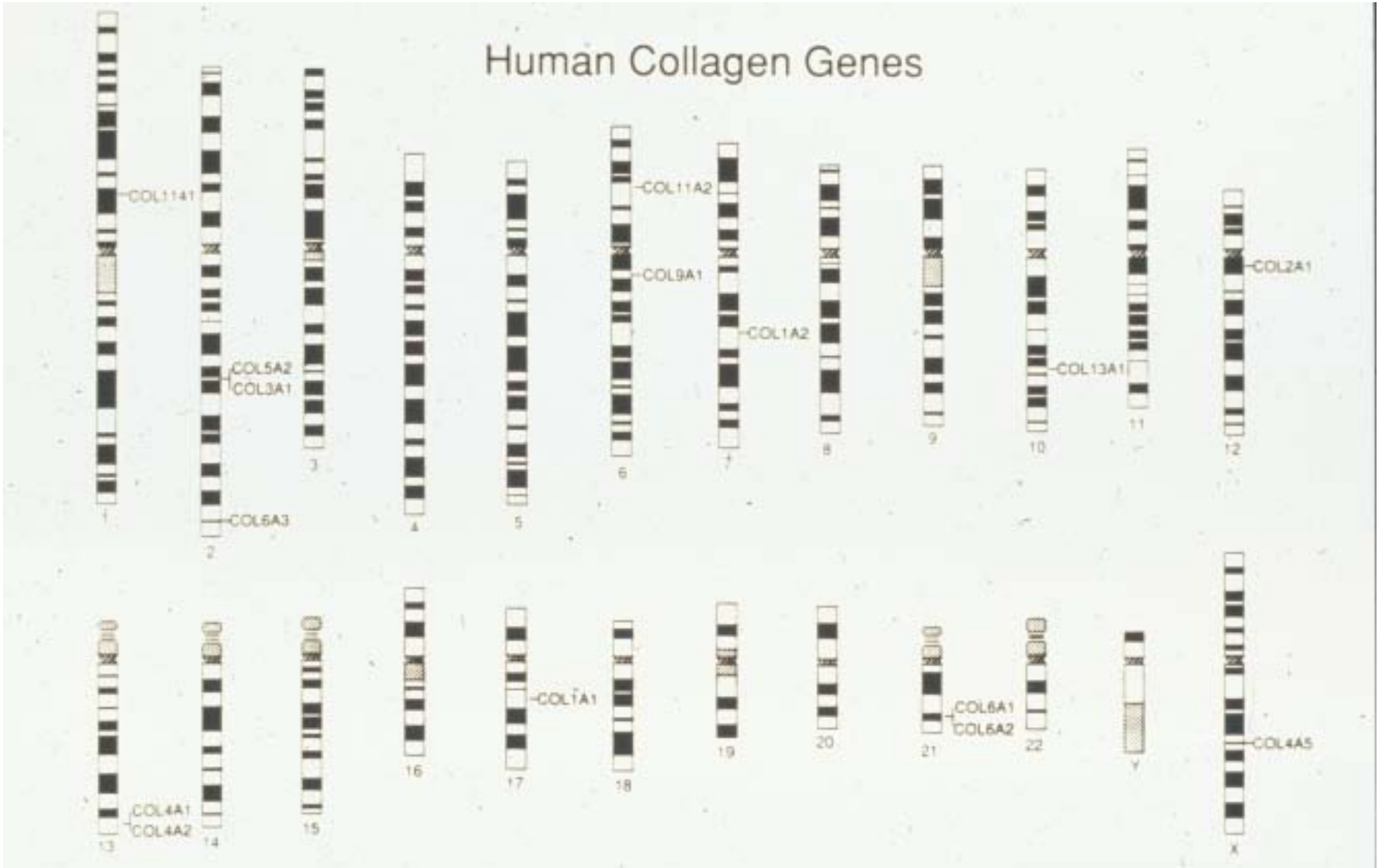
Collagens are the most abundant proteins in the human body, comprising 25-30% of all proteins

Almost 30 different collagens have been identified!

TYPE	TISSUE DISTRIBUTION
	Fibril-forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, fetal skin
	Network-forming
IV	Basement membrane
VII	Beneath stratified squamous epithelia
	Fibril-associated
IX	Cartilage
XII	Tendon, ligaments, some other tissues

Figure 4.2
The most abundant types of collagen.

There are MANY collagen genes throughout the genome



- All collagens are triple-helically structured
- Have the amino acid structure Gly-X-Y
- Rich in (hydroxy)-proline and (hydroxy)-lysine

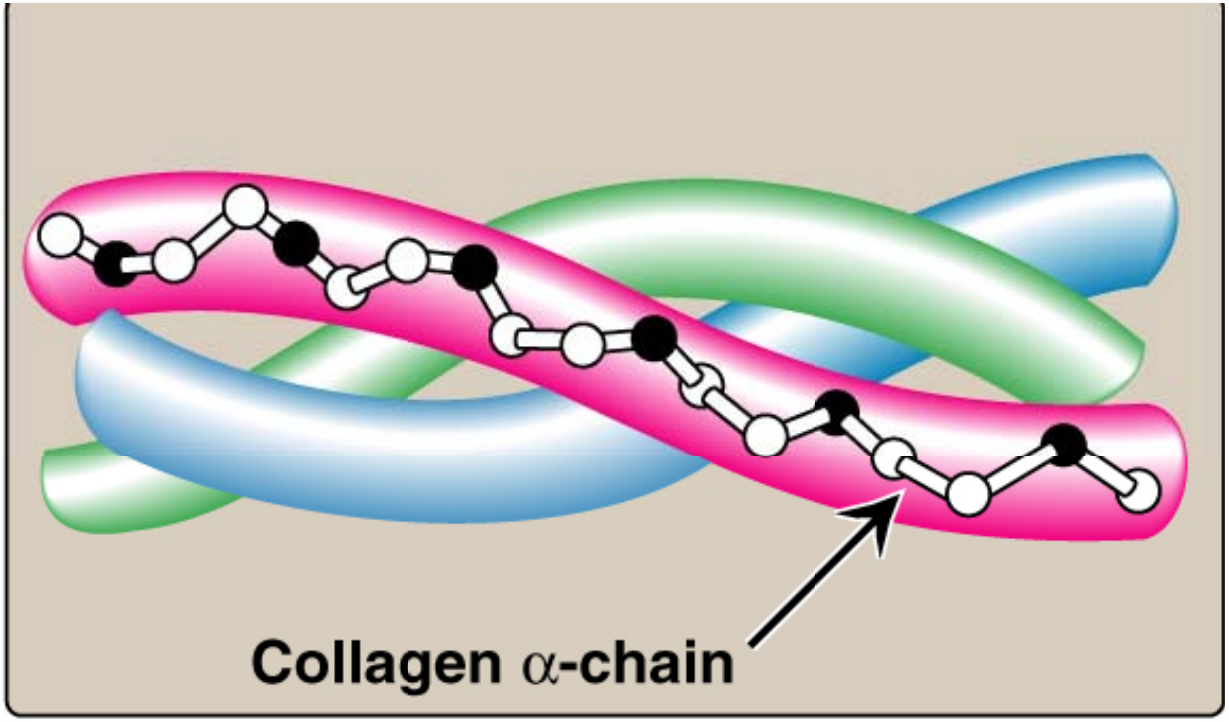
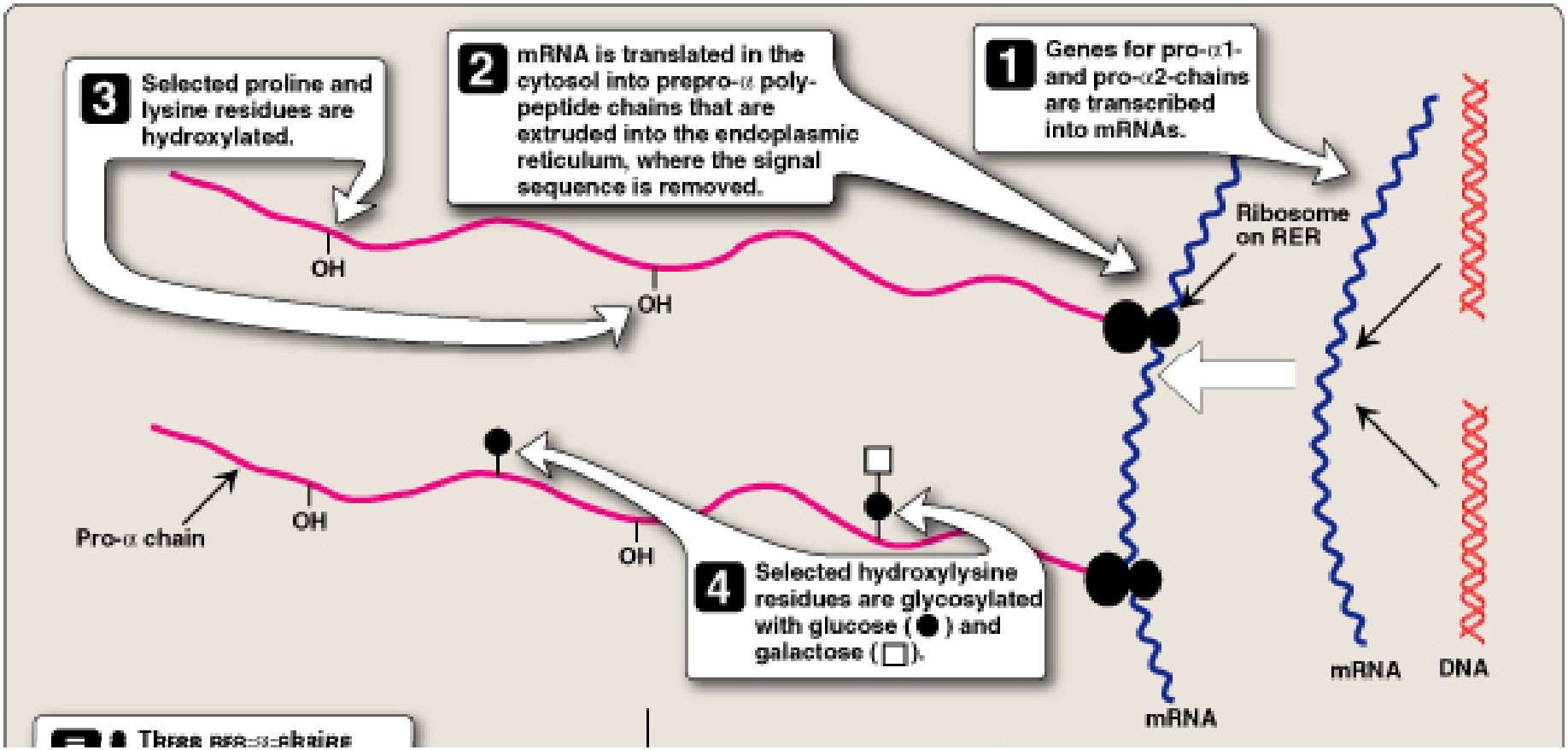


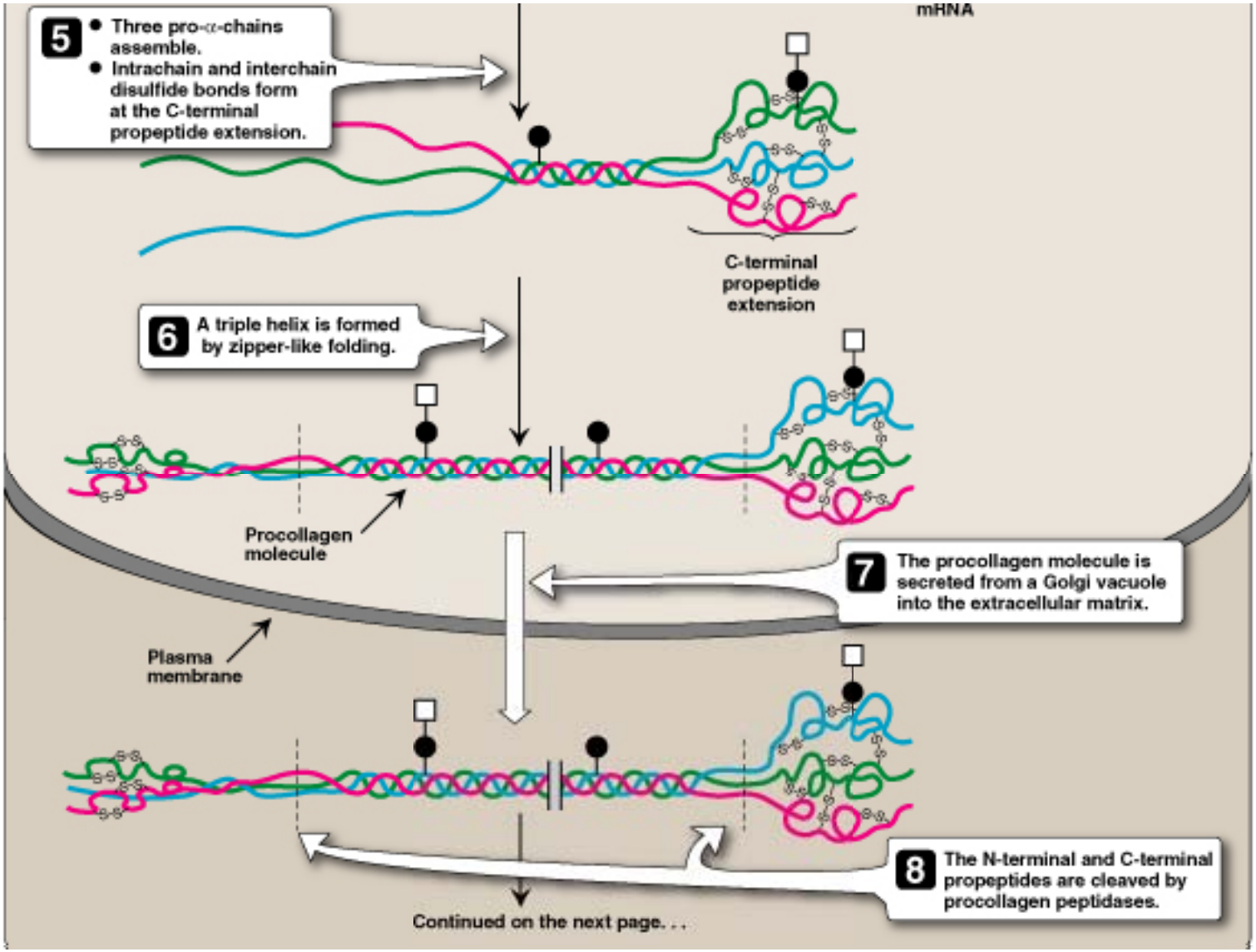
Figure 4.1

Triple-stranded helix of collagen.

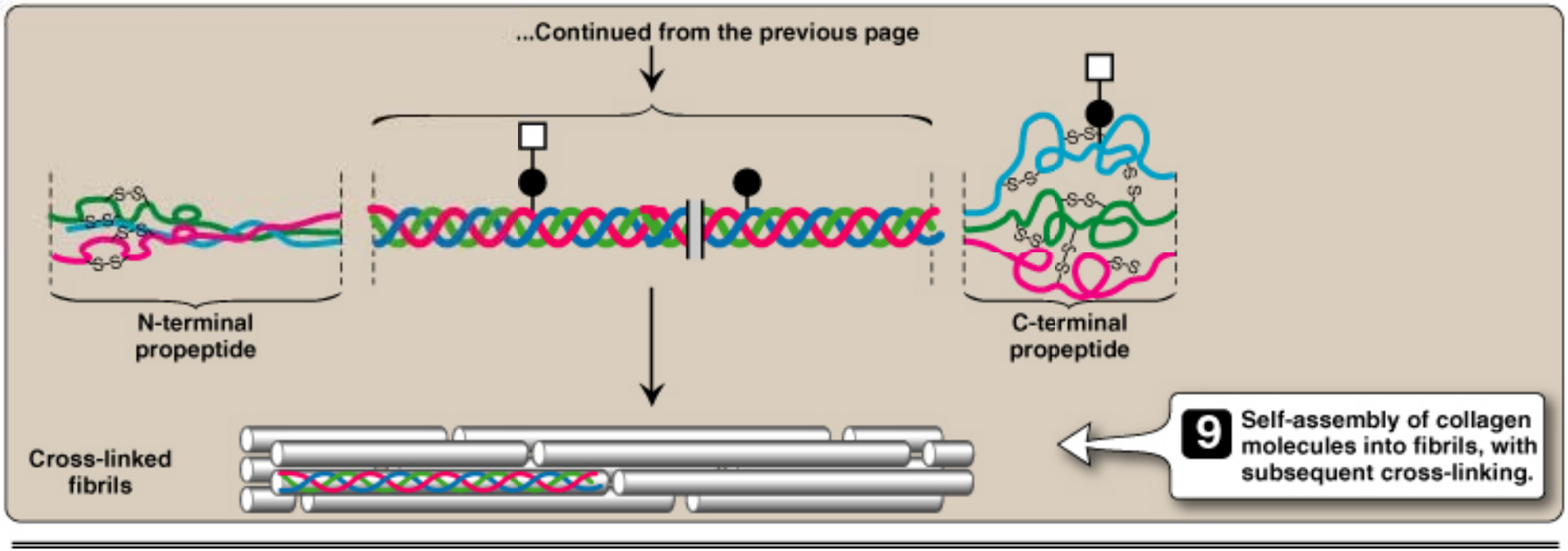
How is collagen made in the cell?



Collagen synthesis, continued….



And finally, assembly of the individual collagen molecules into fibrils



Another view…..

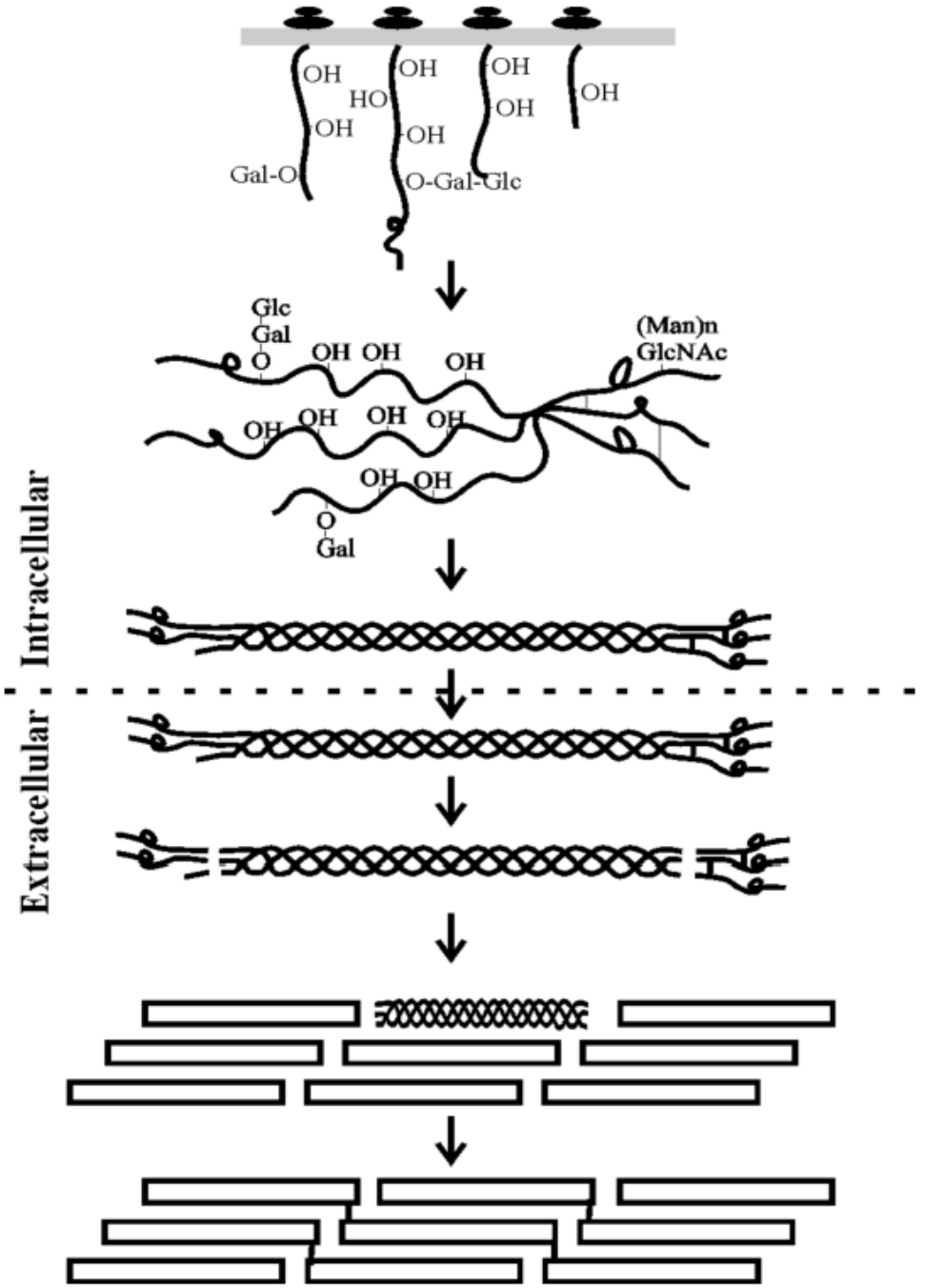
hydroxylation and glycosylation

chain association

secretion

cleavage

assembly into fibrils



Linear polymers of fibrils have a specific banding pattern that comes from the regularly staggered packing of the collagen molecules

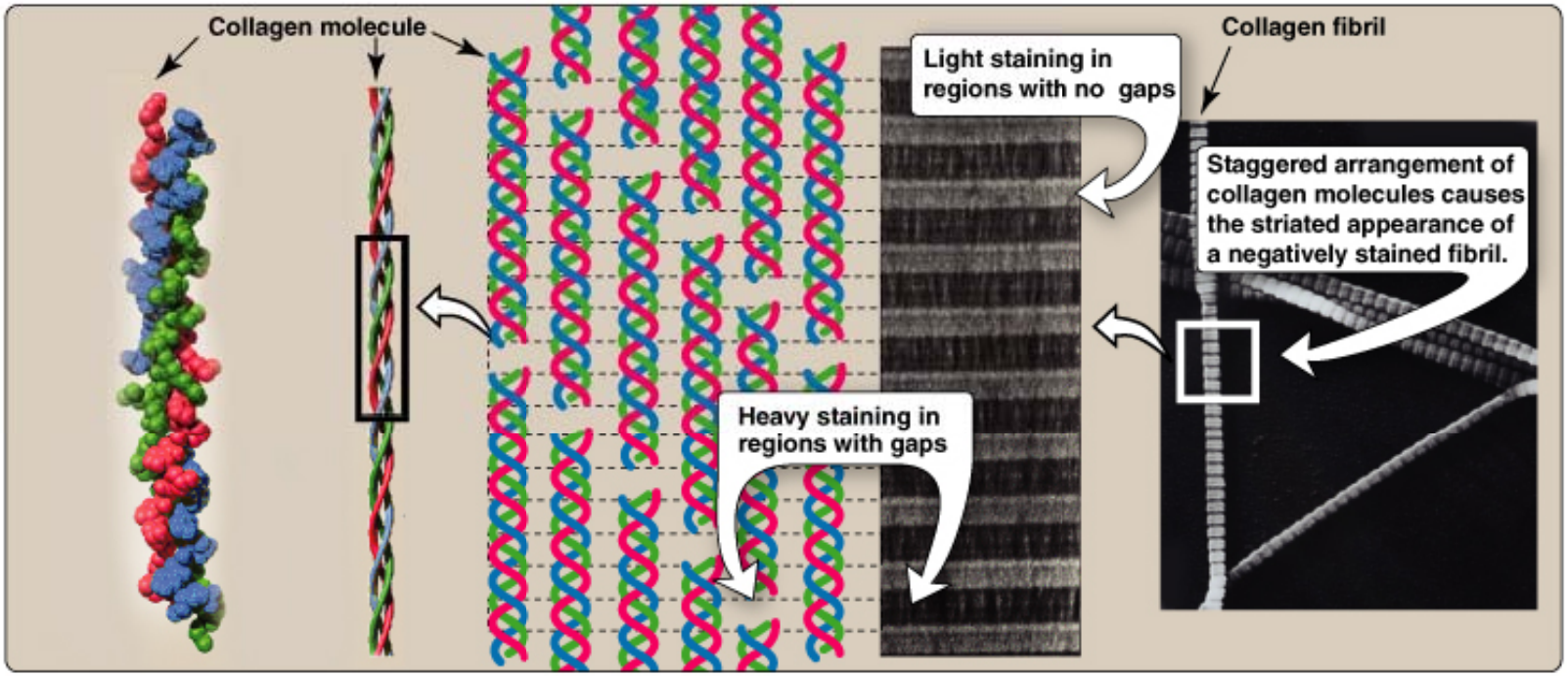
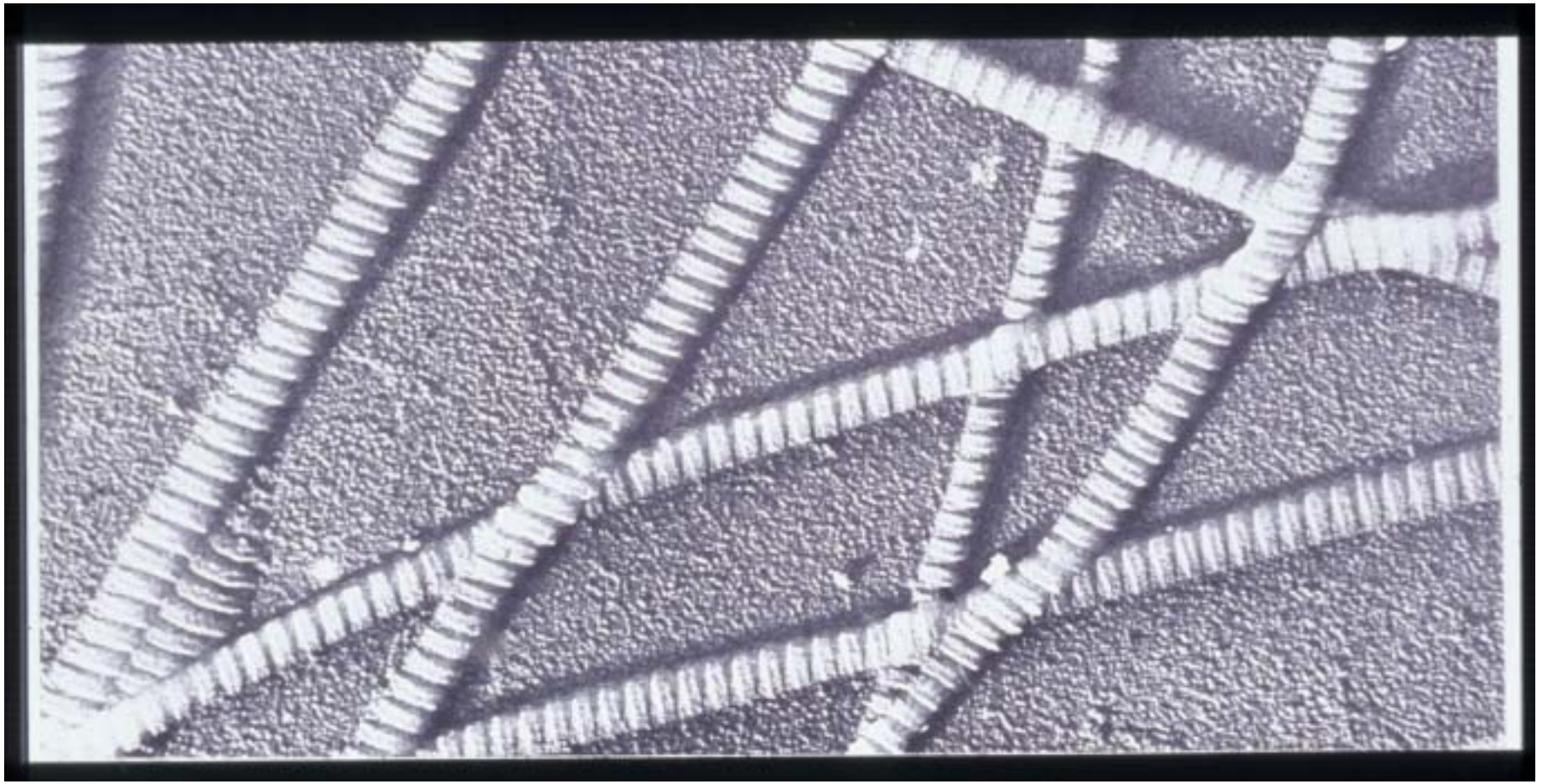


Figure 4.3

Collagen fibrils at right have a characteristic banding pattern, reflecting the regularly staggered packing of the individual collagen molecules in the fibril.

Electron micrograph of collagen fibrils



Proline and lysine residues in collagens are often post-translationally modified by hydroxylation

-the enzymes involved are prolyl hydroxylase and lysyl hydroxylase

-this modification requires Fe^{+2} and vitamin C as cofactors

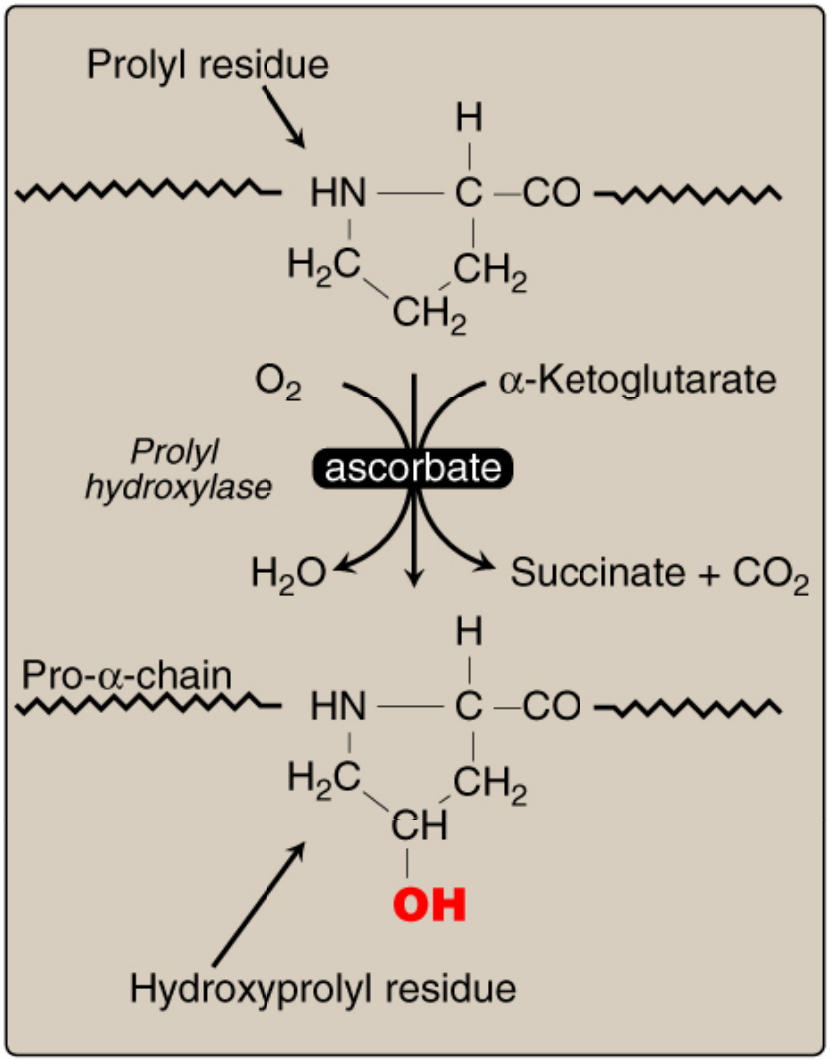


Figure 4.6
Hydroxylation of prolyl residues of pro-α-chains of collagen by *prolyl hydroxylase*.

Collagens are also extensively cross-linked to stabilize the triple helix

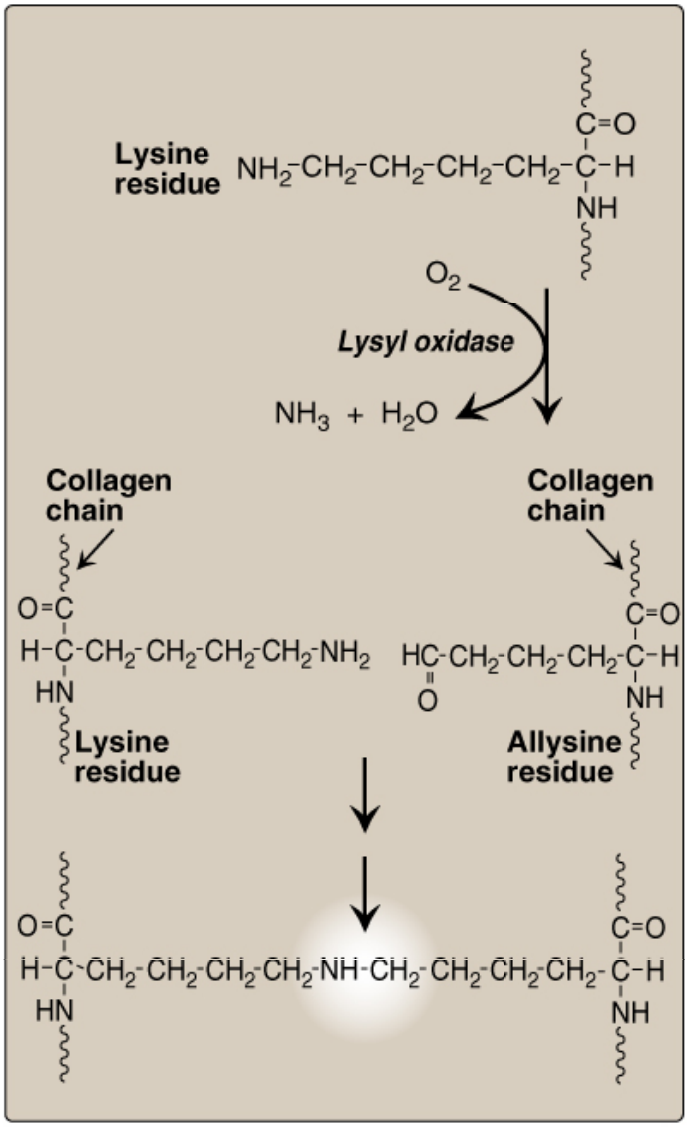
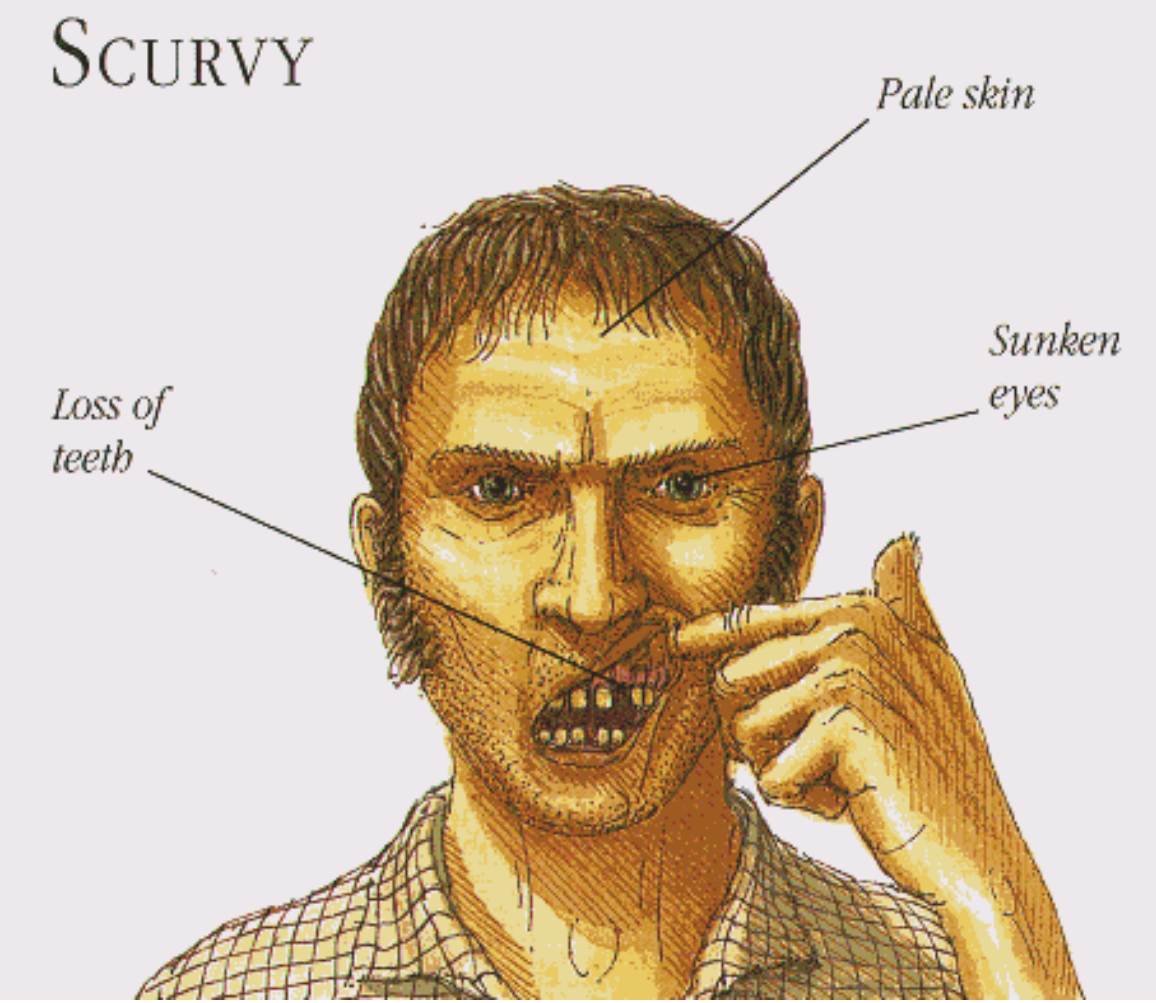


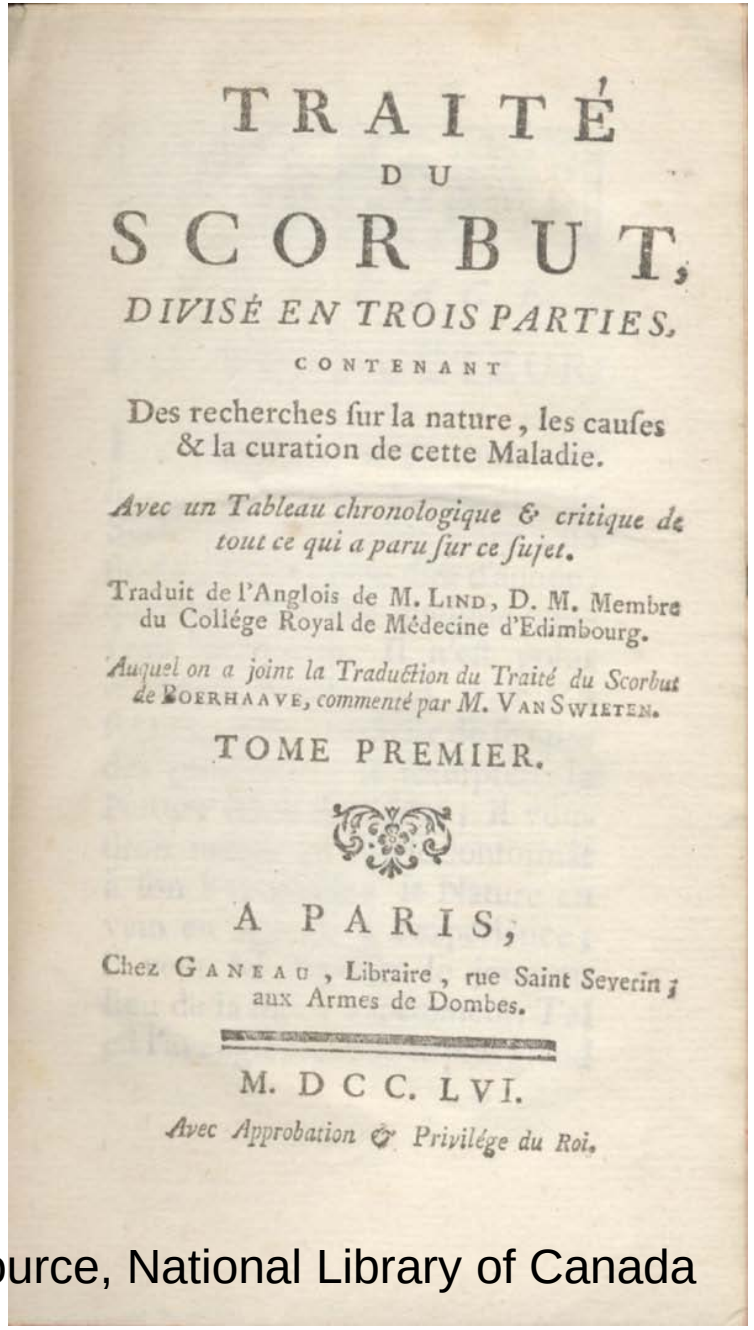
Figure 4.9
Formation of cross-links in collagen.

Scurvy…a non-genetically based collagen disorder….



The first clinical trial!

1747: Dr. James Lind, on a voyage from England to Plymouth, MA divided 12 Scurvy-sick sailors into six groups of two. Each group had the same meals but one group got supplements including oranges and lemons
-the two men who had the citrus fruits recovered immediately



TRAITÉ
DU
SCORBUT,
DIVISÉ EN TROIS PARTIES,
CONTENANT
Des recherches sur la nature, les causes & la curation de cette Maladie.
Avec un Tableau chronologique & critique de tout ce qui a paru sur ce sujet.
Traduit de l'Anglois de M. LIND, D. M. Membre du Collége Royal de Médecine d'Edimbourg.
Auquel on a joint la Traduction du Traité du Scorbut de BOERHAAVE, *commenté par M.* VAN SWIETEN.
TOME PREMIER.
A PARIS,
Chez GANEAU, Libraire, rue Saint Severin; aux Armes de Dombes.
M. DCC. LVI.
Avec Approbation & Privilége du Roi.

1756; source, National Library of Canada

Scurvy frequently presents as easily bruised skin, bleeding gums, loosened teeth, “corkscrew hairs”, poor wound healing

Scurvy is rare now among American adults

Not rare in places in the world where malnutrition is common

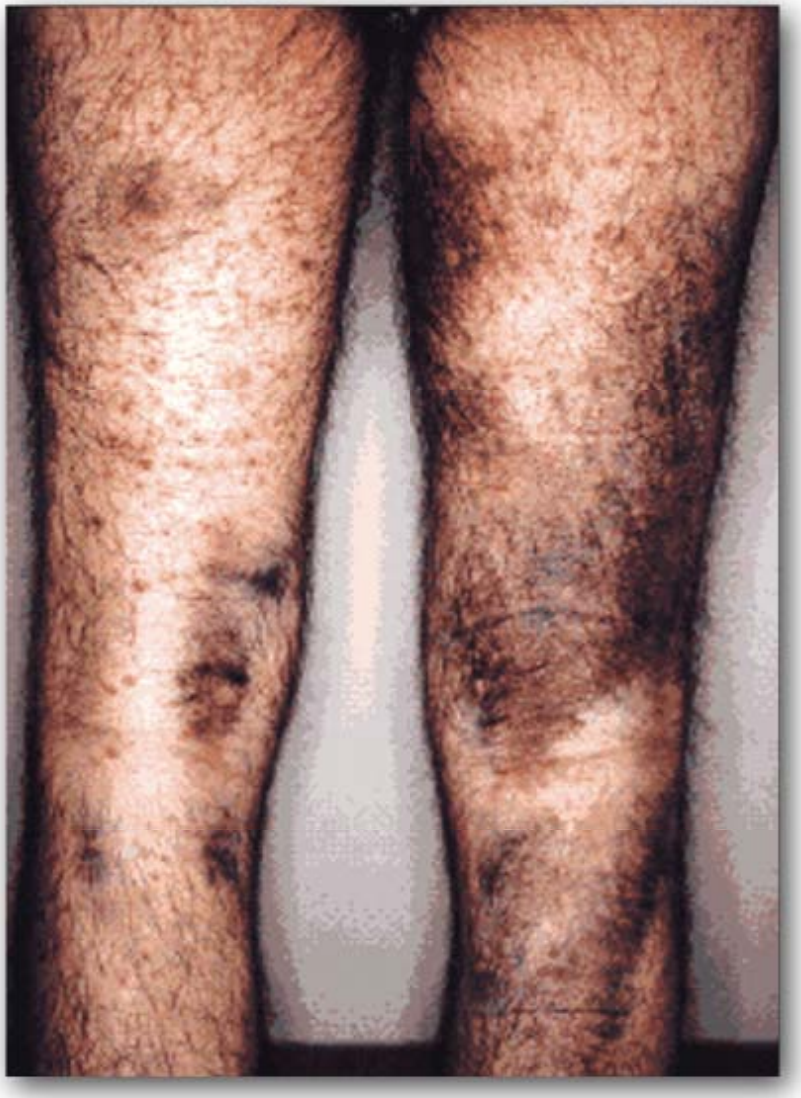


Figure 4.8

The legs of a 46-year-old man with scurvy.

Genetically-based collagen disorders: Osteogenesis imperfecta (OI) and Ehlers-Danlos syndrome

OI is also known as “brittle bone disease” since bones easily fracture

Type I OI: presents in infancy or early childhood

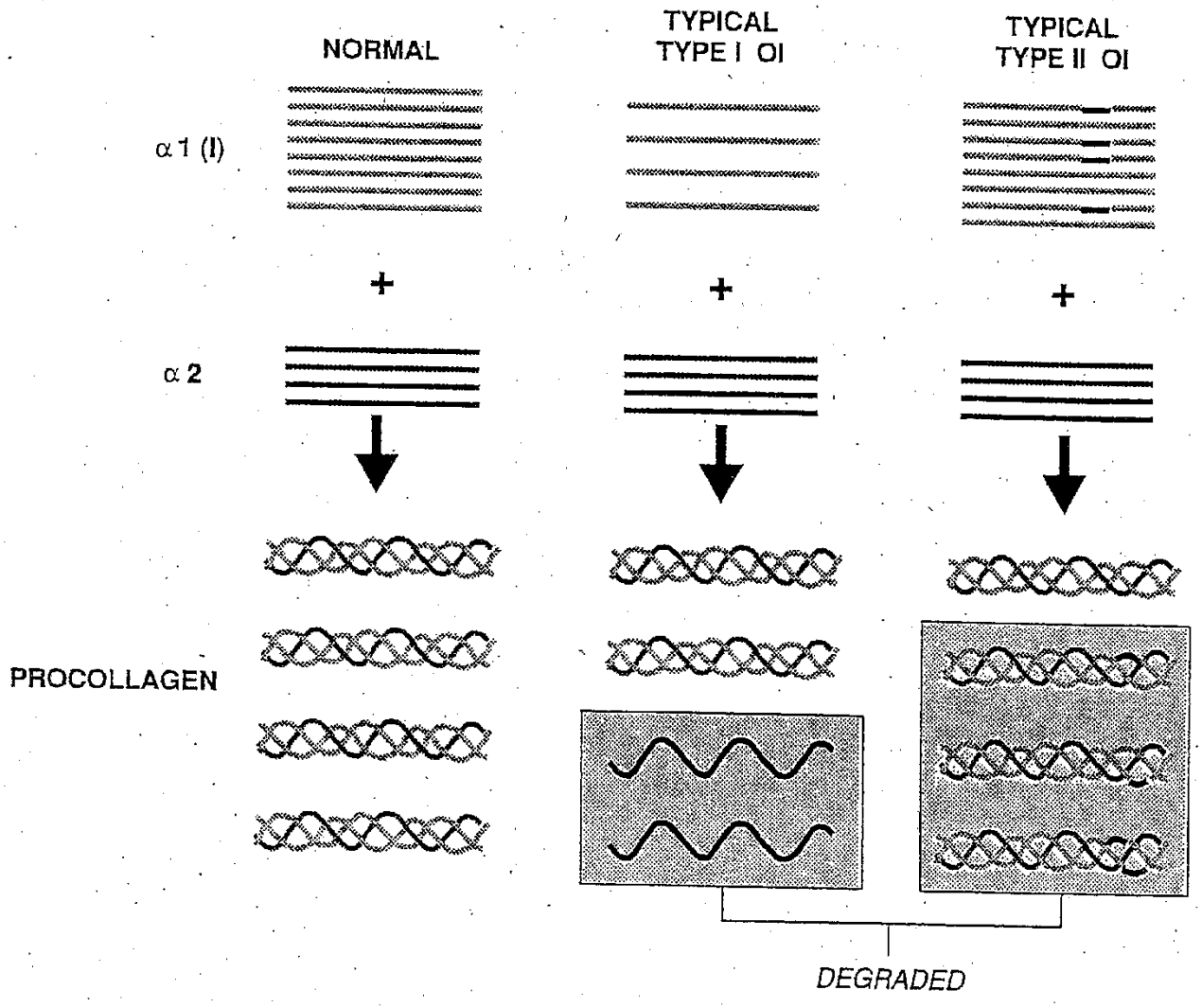
Type II OI: more severe

Most mutations in type II, III and IV result from substitutions in the gene for COL1A1 or COL1A2 that result in the change from Gly to another amino acid with a bulky side chain in type I collagens—this prevents correct folding into the triple helix

Dentiogenesis imperfecta too

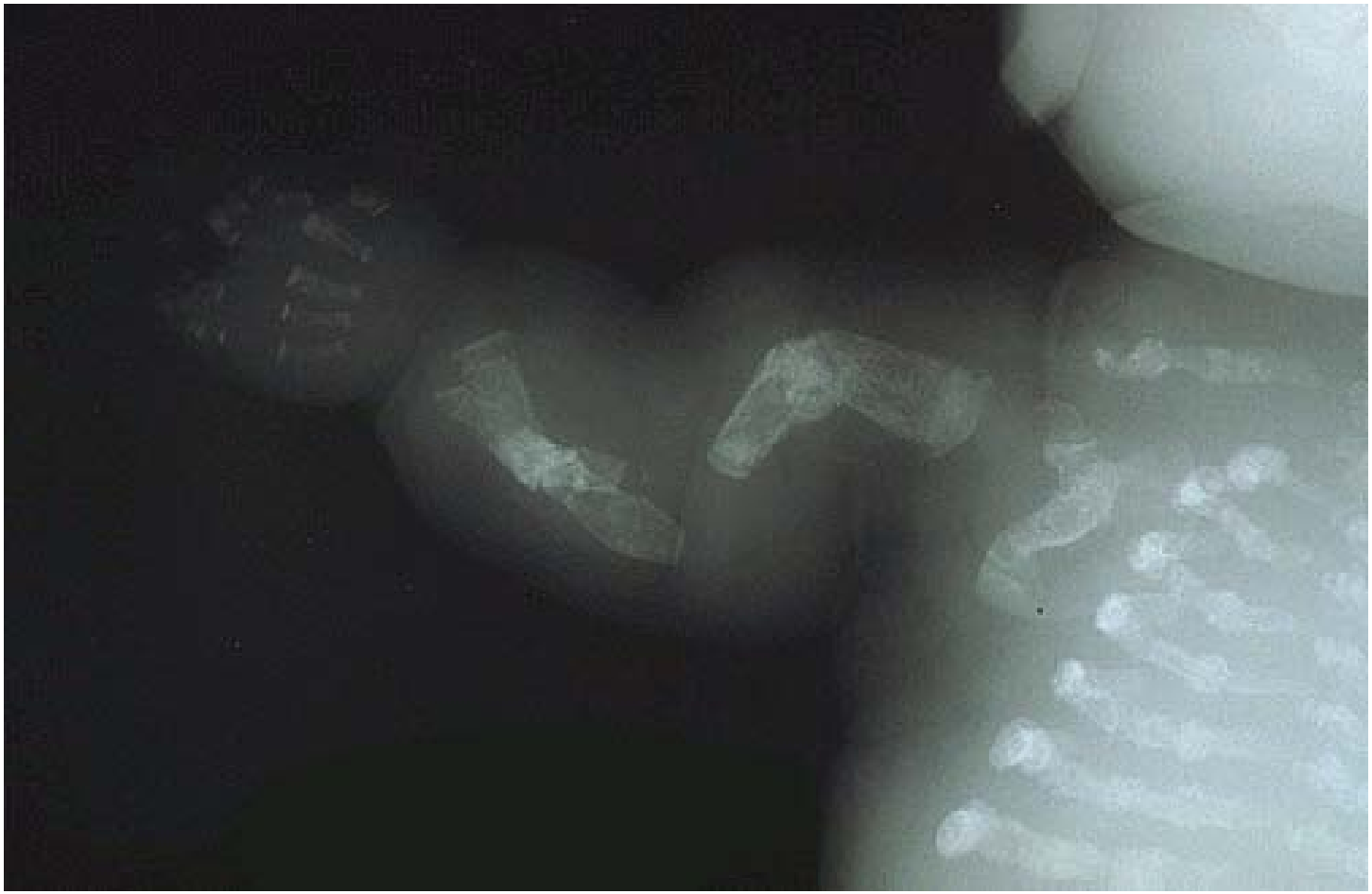
Severity of OI

II>III>IV>I

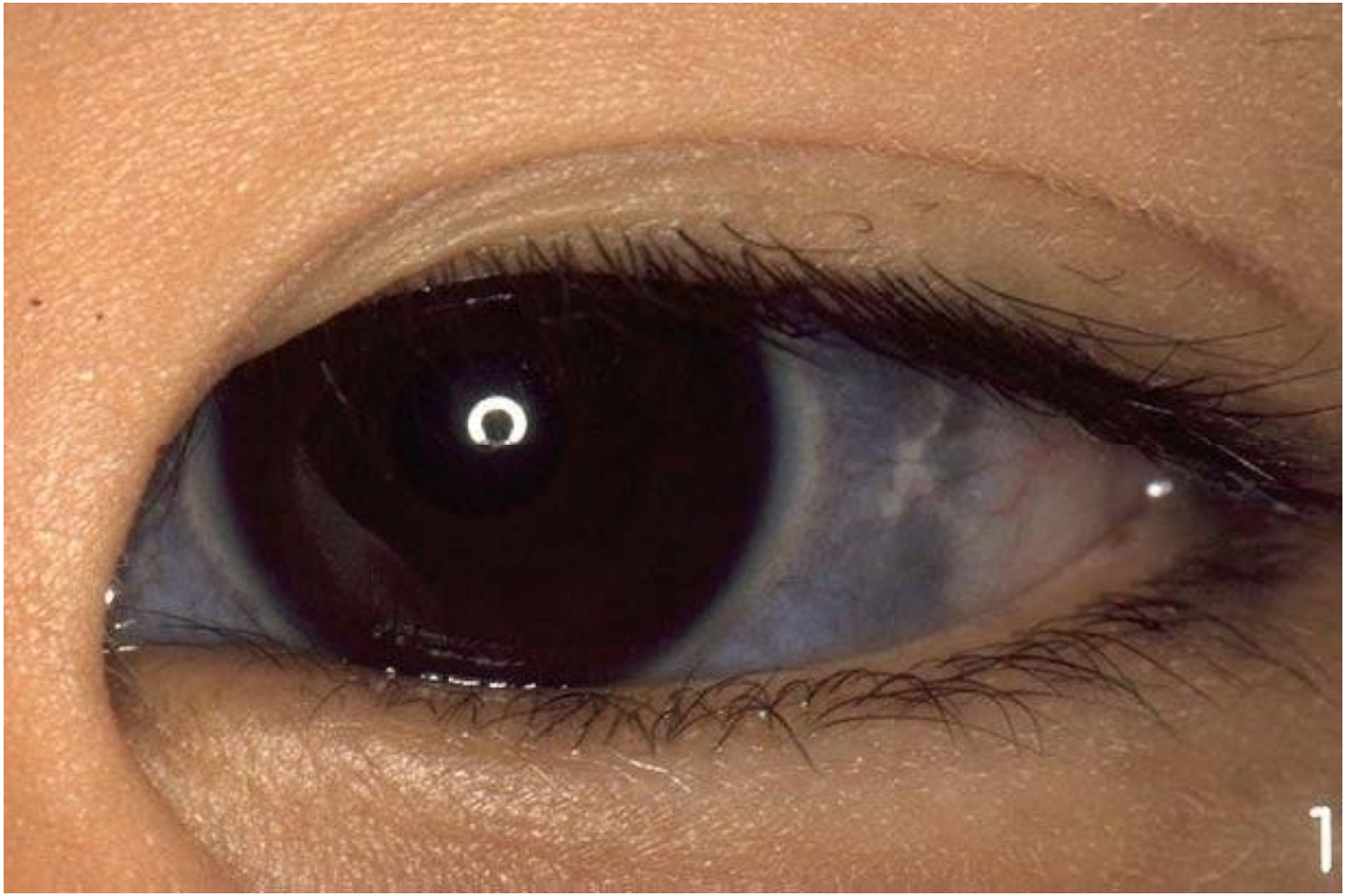


Mutations in collagens have a direct effect on OI

Radiograph of an individual with Type II OI, where fractures appear *in utero*



Blue sclera are common in OI patients



Ehlers-Danlos Syndrome (EDS): A collection of defects

EDS type	Clinical findings	Inheritance	Gene defects
Classic (I/II)	Skin and join hypermob., bruises	AD	COL5A1 or 2
Hypermobility(III)	Joint hypermob., pain	AD	unknown
Vascular(IV)	Arterial or uterine rupture	AD	COL3A1
Kyphoscoliosis(VI)	Joint laxity, ocular fragility, scoliosis	AR	Lysyl-hyroxylase
Arthrochalasia(VIIa,b)	Joint hypermob., scoliosis	AD	COL1A1 or 2
Dermatosparaxsis(VIIc)	Fragile skin, bruising	AR	Procol. N-peptidase

Hypermob.=hypermobility

AD= autosomal dominant, AR=autosomal recessive

Stretchy skin and joint hypermobility are common in EDS

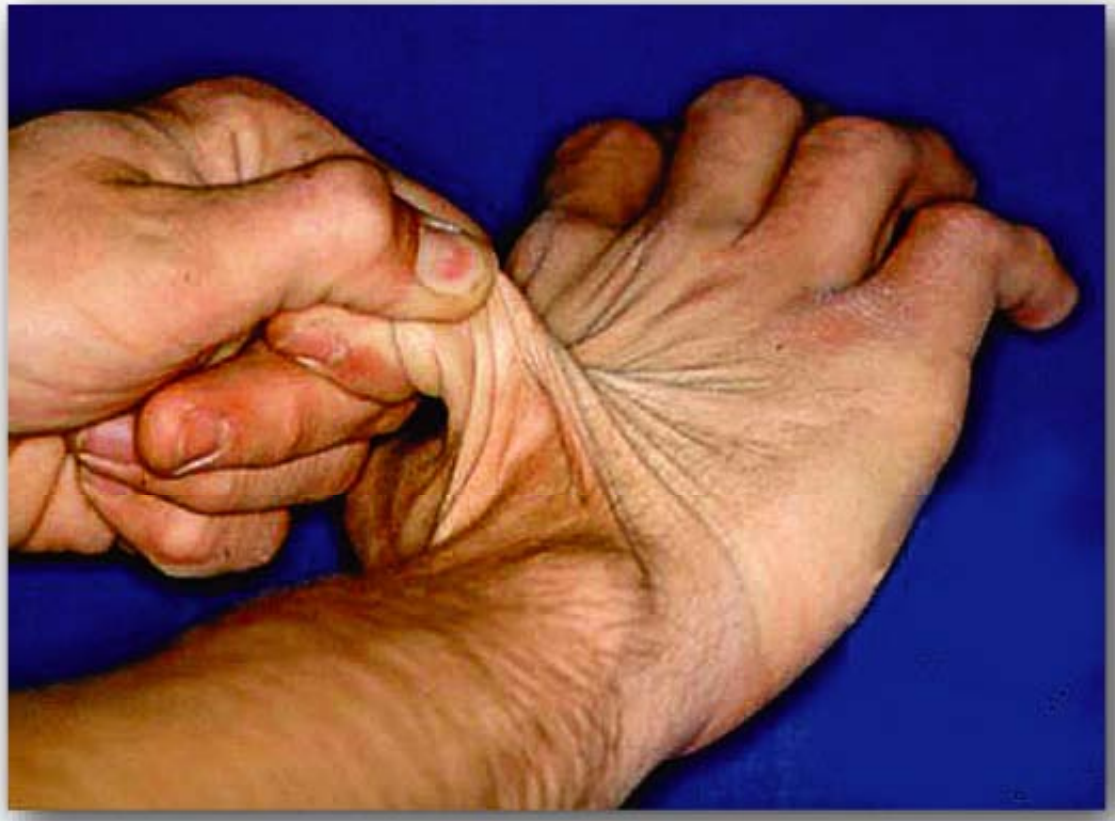


Figure 4.10

Stretchy skin of Ehlers-Danlos syndrome.

Elastin: a rubbery connective tissue protein
-can be stretched to several times their normal length
-found in the walls of large arteries, lungs, and elastic ligaments
-is an insoluble protein polymer synthesized from the precursor, tropoelastin
-only one genetic type unlike collagen
-rich in glycine, proline and lysine, only has a little hydroxyproline and no hydroxylysine
-is secreted by cells into extracellular space
-there it interacts with fibrillin

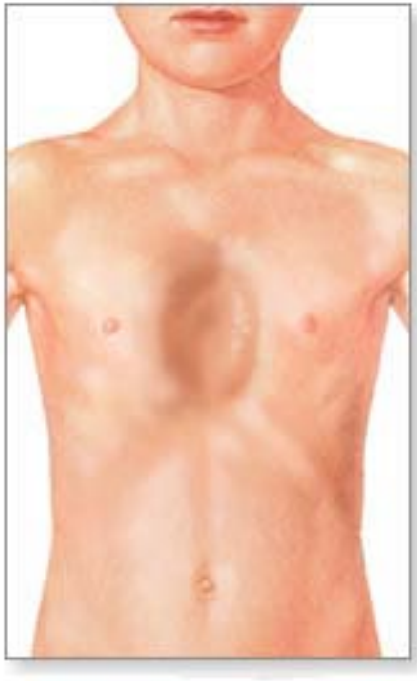
Mutations in fibrillin are responsible for Marfan syndrome

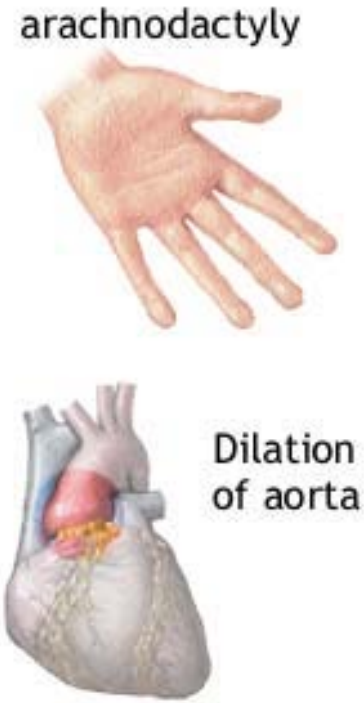
Marfan syndrome is an autosomal dominant disorder that has been linked to the *FBN1* gene on chromosome 15.

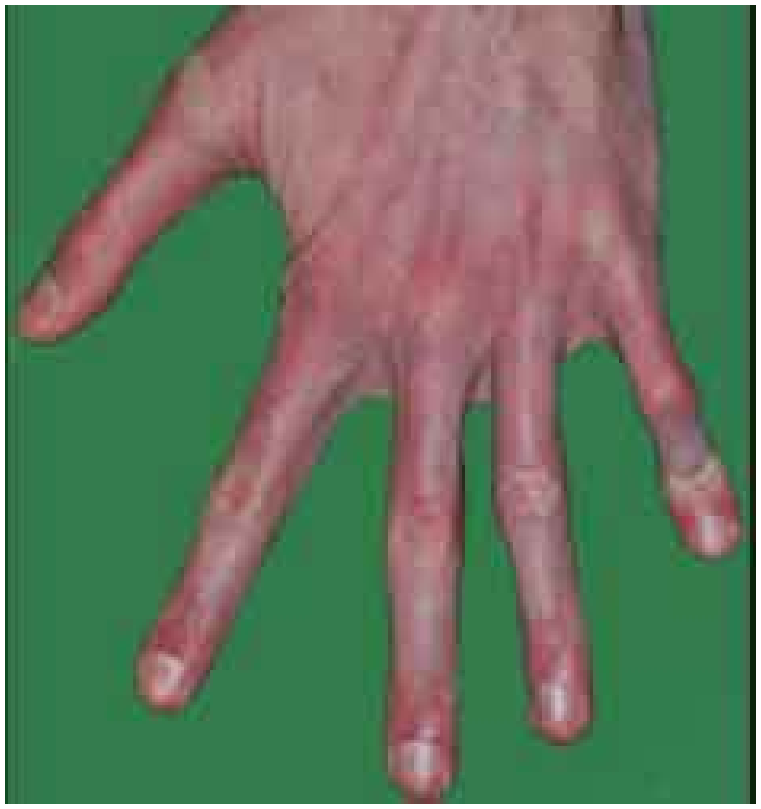
- ***FBN1* encodes a protein called fibrillin, which is essential for the formation of elastic fibers found in connective tissue.**

- **Without the structural support provided by fibrillin, many tissues are weakened, which can have severe consequences, for example, ruptures in the walls of major arteries.**

MARFAN SYNDROME is a connective tissue disorder, so affects many structures, including the skeleton, lungs, eyes, heart and blood vessels.
The disease is characterized by unusually long limbs, and is believed to have affected Abraham Lincoln.







Some of the lysyl side chains are oxidatively deaminated by lysyl oxidase, forming allysine residues.

Three allysine side chains + one unmodified lysyl side chain from the same or nearby polypeptide form a desmosine cross-link.

This cross-linking helps make elastin an extensively interconnected rubbery network

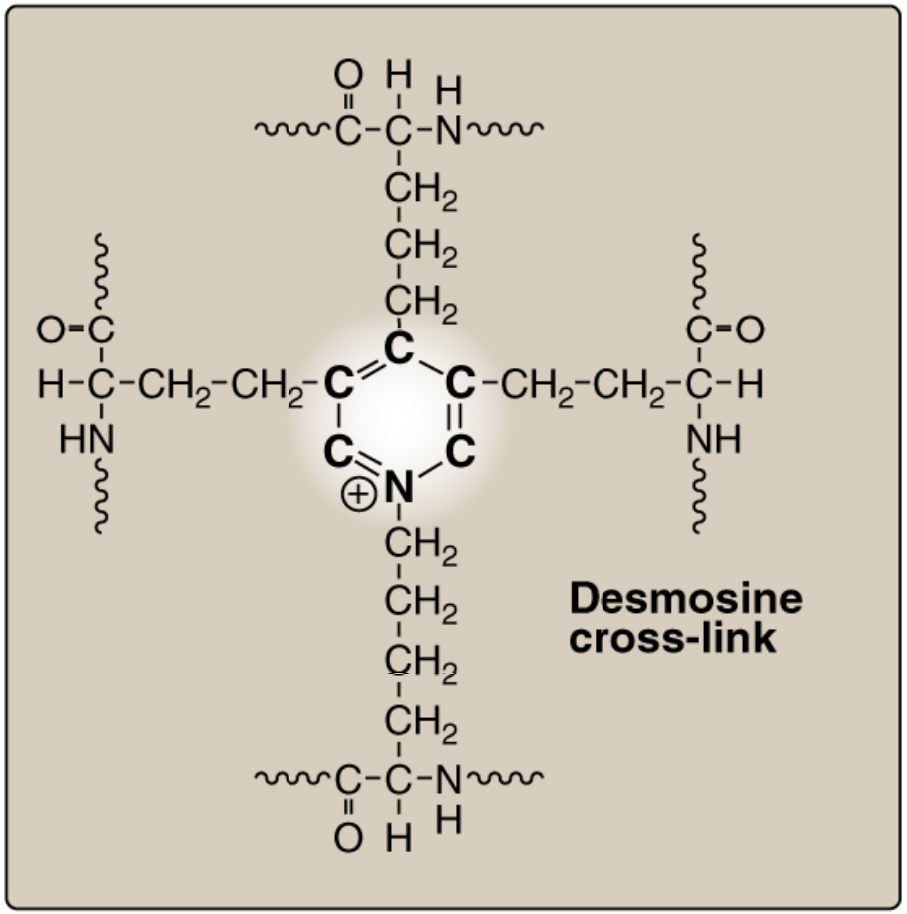


Figure 4.12

Desmosine cross-link in elastin.

Elastin can stretch and bend in any direction, giving connective tissue elasticity

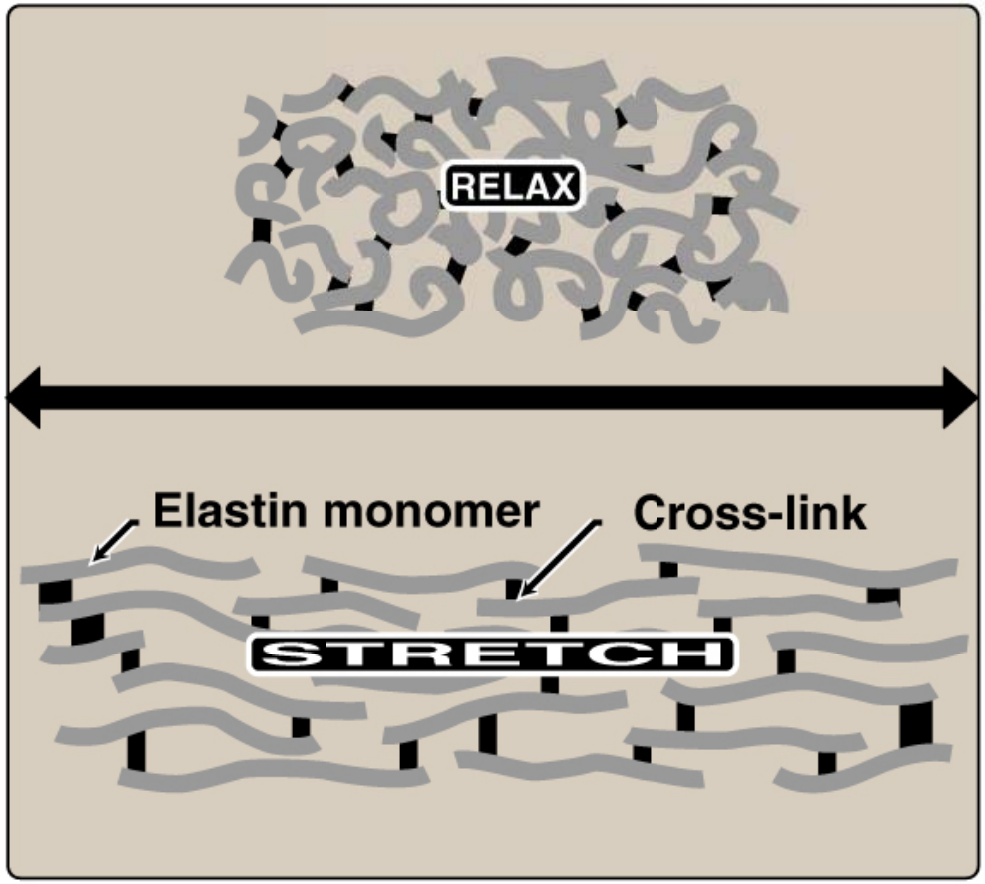


Figure 4.13
Elastin fibers in relaxed and stretched conformations.

Summary

Collagens are highly structured molecules with an abundance of glycine, proline, and lysine that help to give a characteristic three-dimensional, triple-helical structure.

Collagens are the most abundant proteins in the body.

Defects in collagen synthesis can lead to a number of disorders, including scurvy, OI and EDS.

Elastin is a rubbery connective tissue protein that interacts with fibrillin.

Genetic defects in fibrillin can lead to Marfan syndrome.