Natural Materials

TABLE 1 General Properties of Certain Natural Polymers

	Polymer	Incidence	Physiological function
A. Proteins			
	Silk	Synthesized by arthropods	Protective cocoon
	Keratin	Hair	Thermal insulation
	Collagen	Connective tissues (tendon, skin, etc.)	Mechanical support
	Gelatin	Partly amorphous collagen	(Industrial product)
	Fibrinogen	Blood	Blood clotting
	Elastin	Neck ligament	Mechanical support
	Actin	Muscle	Contraction, motility
	Myosin	Muscle	Contraction, motility
B. Polysaccharides			
	Cellulose (cotton)	Plants	Mechanical support
	Amylose	Plants	Energy reservoir
	Dextran	Synthesized by bacteria	Matrix for growth of organism
	Chitin	Insects, crustaceans	Provides shape and form
	Glycosaminoglycans	Connective tissues	Contributes to mechanical support
C. Polynucleotides			
	Deoxyribonucleic acids (DNA)	Cell nucleus	Direct protein biosynthesis
	Ribonucleic acids (RNA)	Cell nucleus	Direct protein biosynthesis

Courtesy R. Zenz

Natural Materials

- Natural polymers offer the advantage of being very similar, often identical, to macromolecular substances in the body.

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  - Little/no problems with toxicity or
  - Stimulation of a chronic inflammatory reaction.
  - Ability to be degraded by natural occuring enzymes (control of lifetime of the implant by chemical modifications is possible).

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  - Frequently quite immunogenic (especially protein-based materials).
  - Technological manipulation is much more elaborate (structurally much more complex than most synthetic polymers).
  - When derived from animal sources:
    - High inter-individual and inter-tissue (!) variation in composition and modification → stringent batch-control required

Courtesy R. Zenz

Natural Materials: Proteins

- Proteins:
  - Frequently significantly immunogenic
    - Collagen (weak immunogenic)
    - Can sometimes be prevented by identification and modification of anti-genic determinants
  - Temperatur-sensitive (processing at room temp.)
  - Natural variability in structure (animal source)
    - Species specificity
    - Tissue specificity

Rigid specifications are required from one batch to the next. Stringent control methods must be used for the raw material. Quite elaborate as most of these materials are not readily water soluble...

Courtesy R. Zenz

Natural Materials: Proteins

- Most of the natural polymers used as biomaterials today are constituents of the extracellular matrix (ECM) of connective tissues such as:
  - Tendons
  - Ligaments
  - Skin
  - Blood vessels
  - Bone

- Composites of collagen and elastin fibers encasing a matrix of proteoglycycanes with extensive intermolecular chemical bonding; highly swollen in water.

Courtesy R. Zenz

Natural Materials

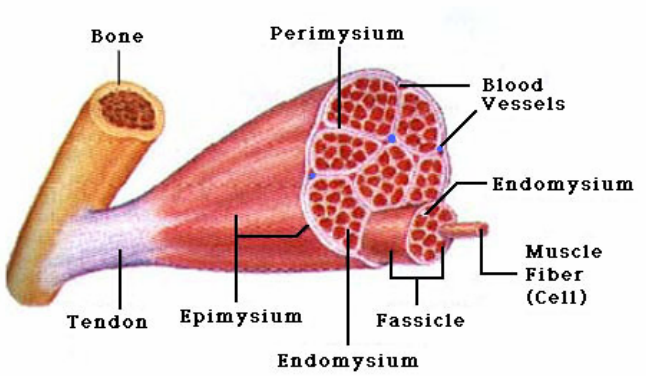
- Naturally occurring composites are within us all. On the macro scale, soft and hard tissues are formed from a complex structural array of organic fibers and matrix.
- Soft tissues are formed from:
  - elastic (elastin) and
  - non-elastic fibers (collagen) with a
  - cellular matrix between the fibers.

Tissue	Tensile Strength (MPa)	Ultimate Elongation (%)
Tendon (low elastin content)	53.0	9.4
Skin (High elastin content)	7.6	78.0
Elastin	1	100
Collagen	50-100	10

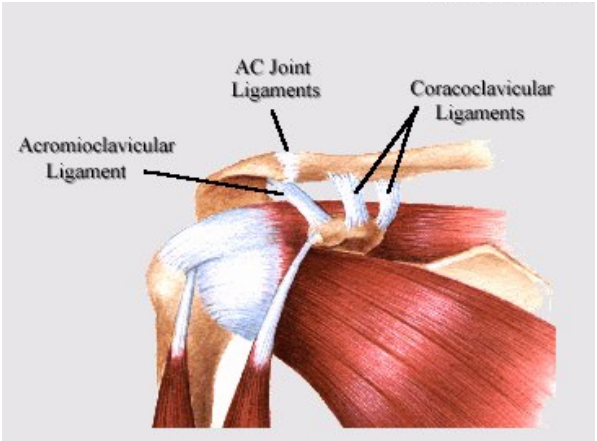
Courtesy R. Zenz

Natural Materials: Soft tissues

- Biological structures such as tendon, linking muscles to bone, are low in elastin thus allowing muscle movement to be translated to the bone.

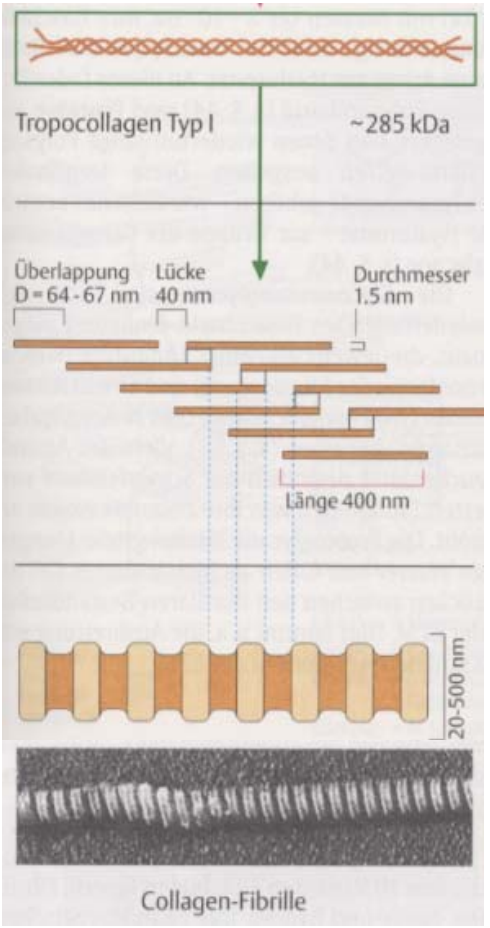


- Ligaments, linking bone to bone, are high in elastin allowing movement between bones but retaining sufficient support to stop joints dislocating.



Collagen

- Collagen: highly abundant and varied protein with more than 14 types discovered.
  - Formed from tropocollagen molecules.
  - Tropocollagen is formed from three peptide chains (1/3 Gly, 1/3 Pro and hydroxyproline and 1/3 other amino acids).
  - Different collagen types are formed by variations in the sequence and amount of amino acids found in the alpha-chains.
  - The three chains are principally stabilized by hydrogen bonds and some occasional covalent bonds forming a right-handed helix.



Courtesy R. Zenz

Collagen

Table 19–4 Some Types of Collagen and Their Properties

	Type	Molecular Formula	Polymerized Form	Tissue Distribution
FIBRIL-FORMING (FIBRILLAR)	I	$[\alpha1(I)]_2\alpha2(I)$	fibril	bone, skin, tendon, ligaments, cornea, internal organs (accounts for 90% of body collagen)
	II	$[\alpha1(II)]_3$	fibril	cartilage, intervertebral disc, notochord, vitreous humor of the eye
	III	$[\alpha1(III)]_3$	fibril	skin, blood vessels, internal organs
	V	$[\alpha1(V)]_2\alpha2(V)$	fibril (with type I)	as for type I
	XI	$\alpha1(XI)\alpha2(XI)\alpha3(XI)$	fibril (with type II)	as for type II
FIBRIL-ASSOCIATED	IX	$\alpha1(IX)\alpha2(IX)\alpha3(IX)$ with type II fibrils	lateral association	cartilage
	XII	$[\alpha1(XII)]_3$ with some type I fibrils	lateral association	tendon, ligaments, some other tissues
NETWORK-FORMING	IV	$[\alpha1(IV)_2\alpha2(IV)$	sheetlike network	basal laminae
	VII	$[\alpha1(VII)]_3$	anchoring fibrils	beneath stratified squamous epithelia

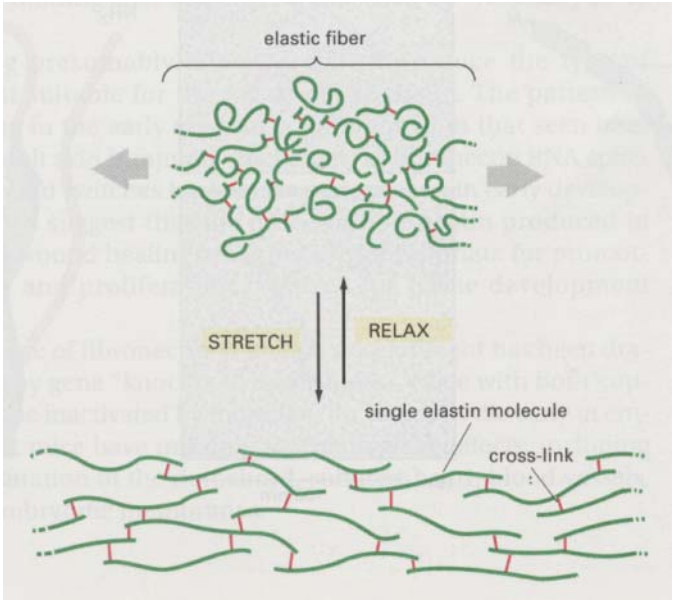
Note that types I, IV, V, and XI are each composed of 2 or 3 types of α chain, whereas types II, III, VII, and XII are composed of only 1 type of α chain each. Only 9 types of collagen are shown, but about 15 types of collagen and about 25 types of α chain have been defined so far.

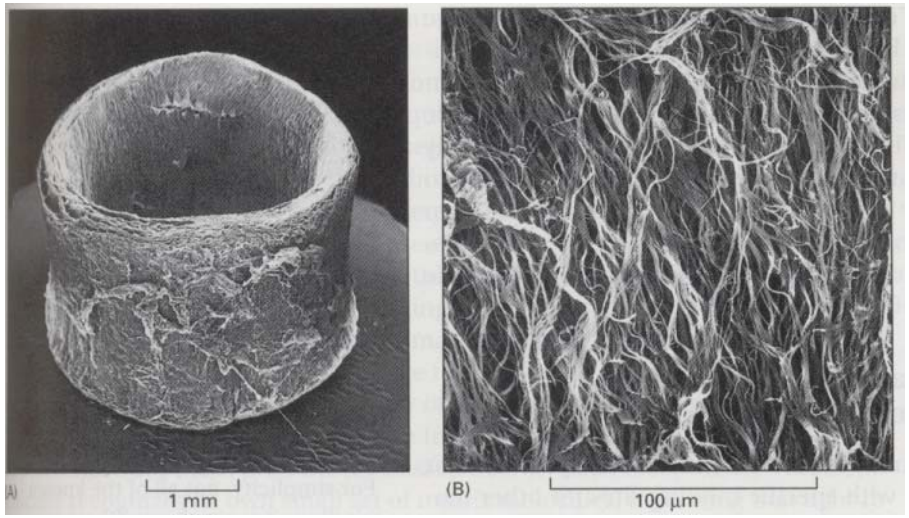
Courtesy R. Zenz

Elastin

- Elastin is formed in a similar fashion to that of collagen.
- Gly, Ala and Ser (55-70%).
- Elastin lacks collagen's repetitive sequencing at the fibril stage.
- Fibres are only 5 to 7mm in length.
- Highly hydrophobic and elastic.

Soluble preparations not yet applied extensibly as bio-mats

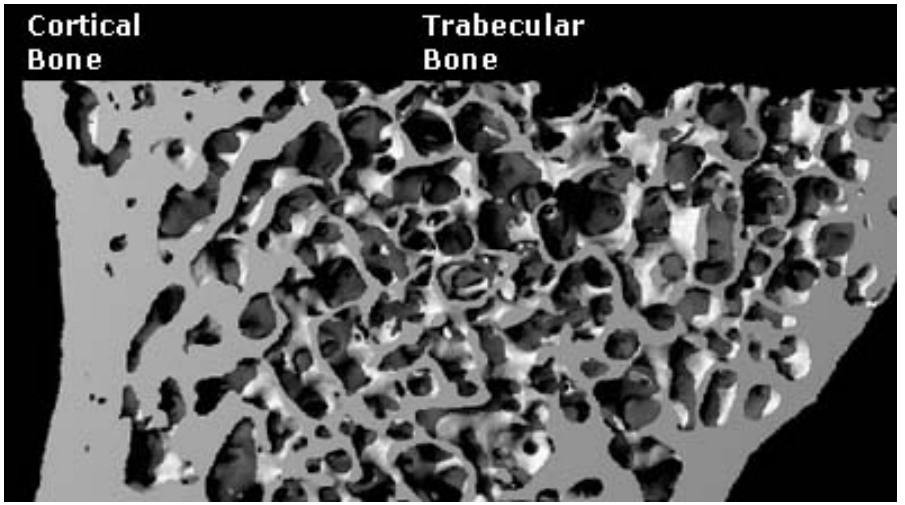




Dog aorta with elastic fibers in the outer layer of the blood vesel.

Natural Materials: Hard tissues

- Bone:
  - Cortical (also called compact)
  - Trabecular (also called cancellous or spongy)



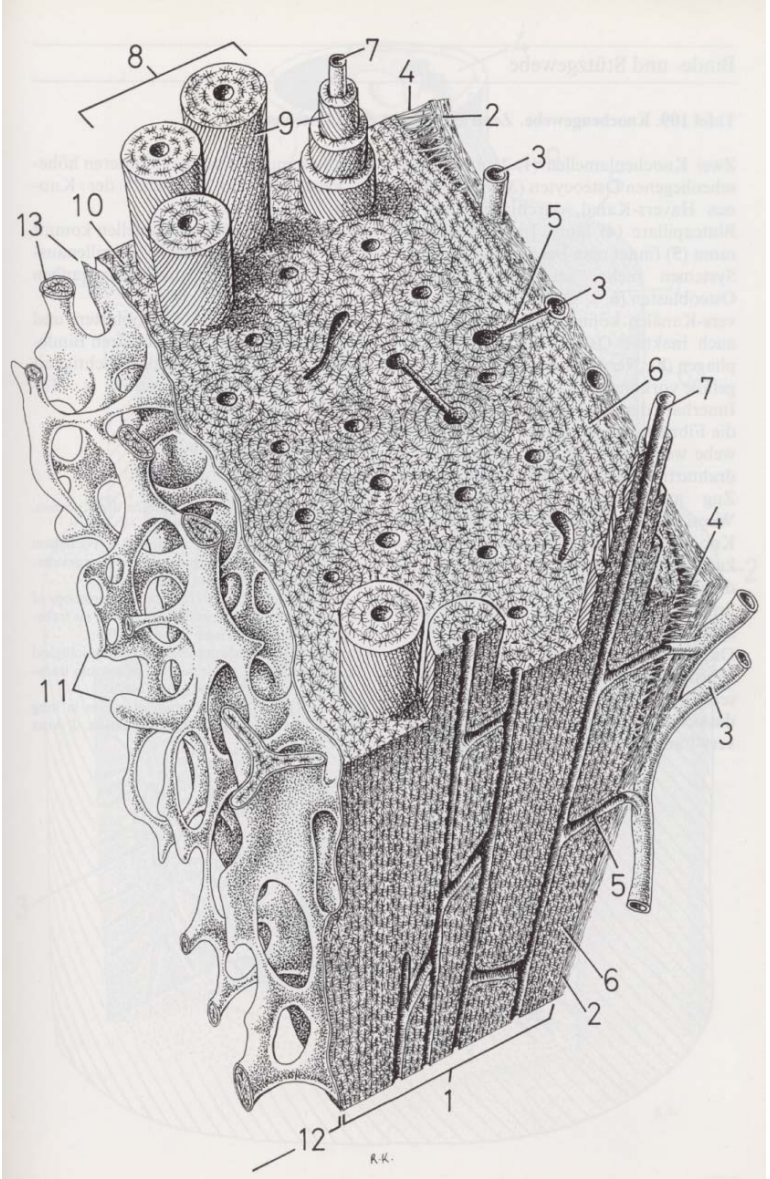
- All hard tissues are formed from the 4 basic phases. The relative fraction varies between bone type and conditions; for typical cortical bone:
  - Organic – colagen fibres (tyype 1) 16%
  - Mineral – Hydroxyapatite 60%
  - Ground substance 2%
  - Water 22%

Courtesy R. Zenz

Hard tissues: Bone

- Trabecullar bone is a sponge like structure; approximates to an isotropic material.

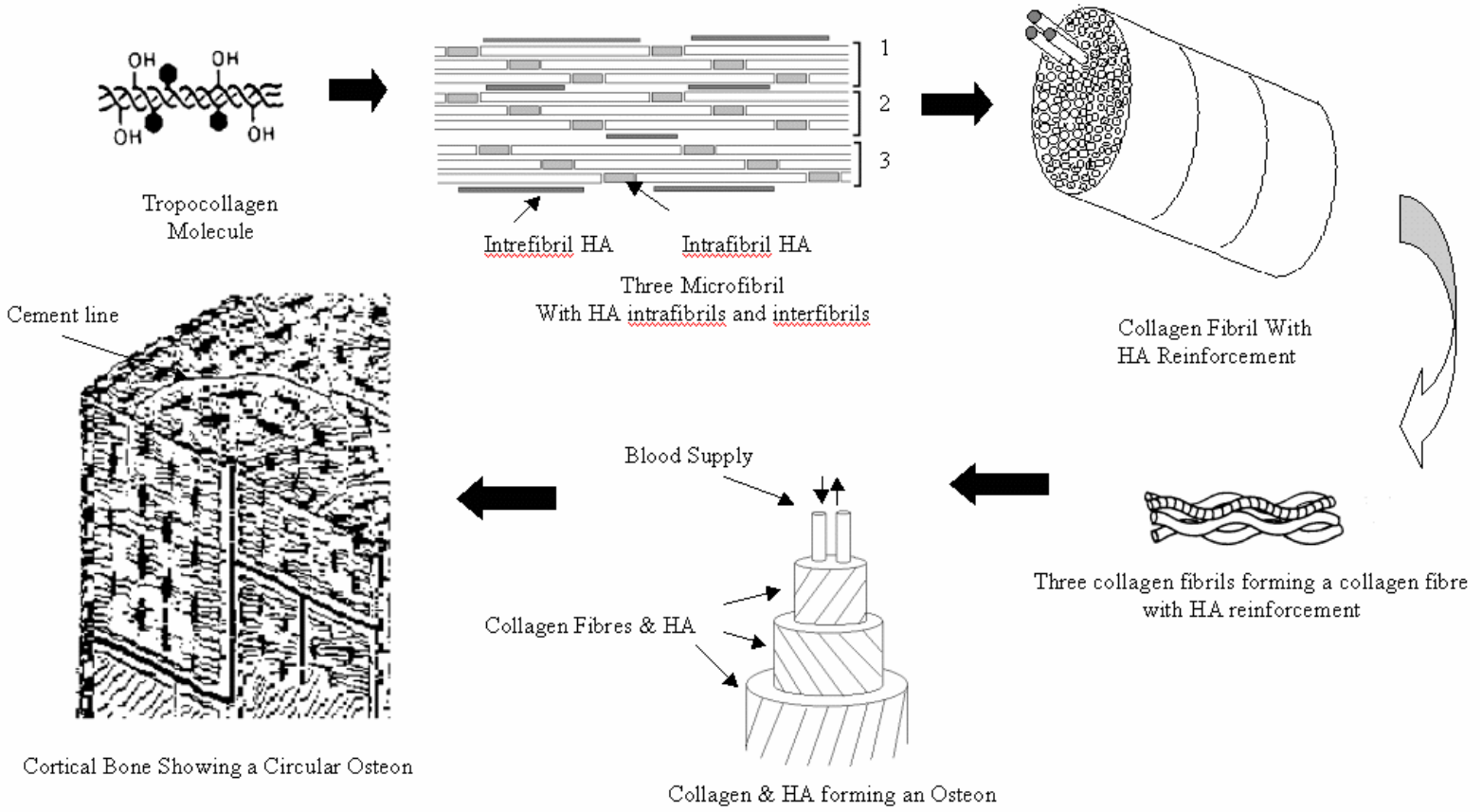
- Cortical bone is highly aniso-tropic with reinforced structures along its loading axis and a highly organized blood supply (haversian system).



Courtesy R. Zenz

Hard tissues: Bone

- Collagen fibres provide the framework and architecture of bone, with the HA partivles located between the fibres. Ground substance (proteins, polysaccharides, mucopolysaccharides act as cement, filling the space between fibres and HA mineral.



Modification of Collagen

- Implanted collagen is subjected to degradative attack by collagenases.
  - Collagenases are naturally present in healing wounds.
  - Degrade collagen and ECM (extracellular matrix).
  - In parallel de novo synthesis of these components occur; are not a replica of the intact tissue: new architectural arrangements lead to scar formation.

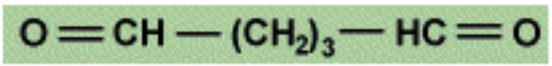
Courtesy R. Zenz

Modification of Collagen

- Modification of collagen is used to accelerate or slow down the degradation rate to a desired level.

- Amino acid residues of collagen can be modified:
  - Carboxylated side groups (Glu, Asp)
  - Amino groups (Lys, Hydroxy-Lys, Arg)
  - Hydroxy groups (Tyr, Hydroxy-Lys)

- Chemical cross-linking is used to decelerate the degradation rate:
  - Dialdehydes (e.g. Glutaraldehyde) is cross-linking ε-amino groups of Lys.



Glutaraldehyde

Courtesy R. Zenz

Collagen-based biomaterials

- Clinical significance of collagen immunogenicity:

  has been shown to be very low: Only small species differences (e.g. cow vs. human)

- Blood clotting effect:

  Fully folded (quarternary helix structure) collagen binds blood-platelets (hemostatic property) partially unfolded collagen (can be achieved by thermo/chemical modifications) is without effect on blood clotting.

TABLE 2 Certain Applications of Collagen-Based Biomaterials

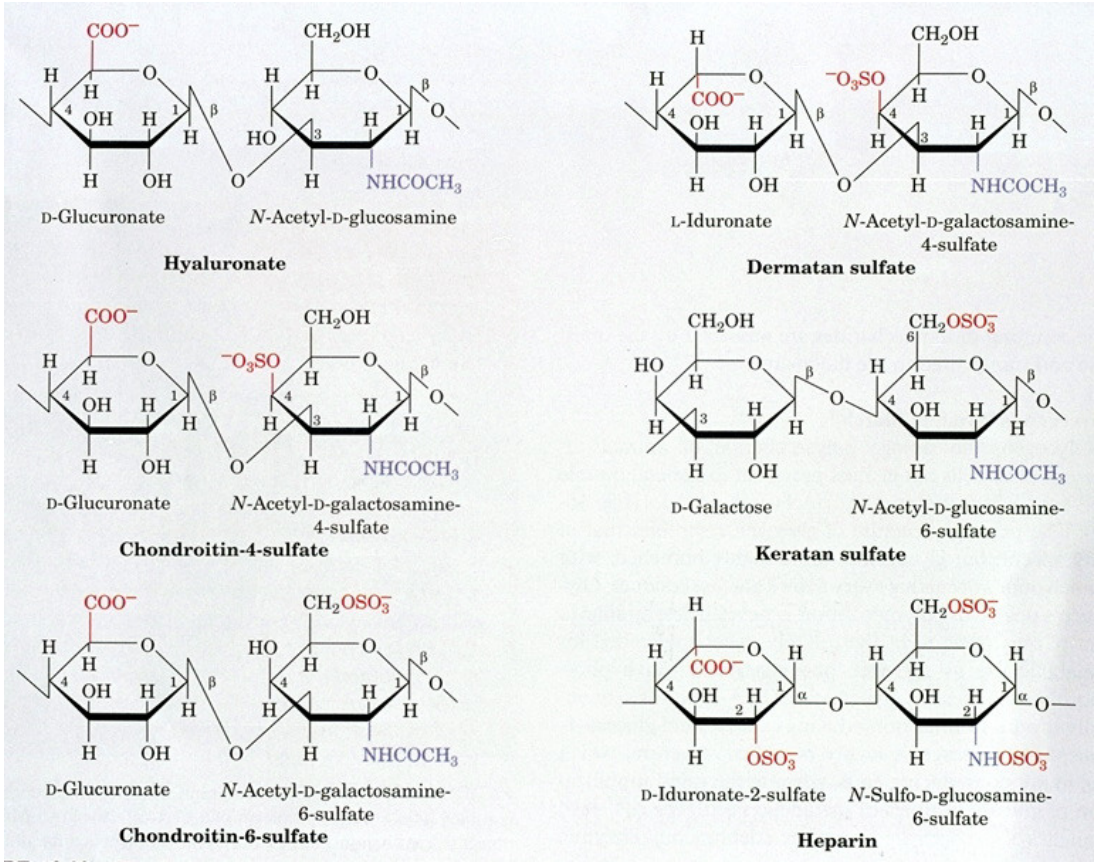
Application	Physical state
Sutures	Extruded tape (Schmitt, 1985)
Hemostatic agents	Powder, sponge, fleece (Stengel *et al.*, 1974; Chvapil, 1979)
Blood vessels	Extruded collagen tube, processed human or animal blood vessel (Nimni, 1988)
Heart valves	Processed porcine heart valve (Nimni, 1988)
Tendon, ligaments	Processed tendon (Piez, 1985)
Burn treatment (dermal re-generation)	Porous collagen-glycosaminoglycan (GAG) polymer[a] (Yannas *et al.*, 1981, 1982, and 1989)
Peripheral nerve regeneration	Porous collagen-GAG copolymer (Chang and Yannas, 1992)
Meniscus regeneration	Porous collagen-GAG copolymers (Stone *et al.*, 1989)
Intradermal augmentation	Injectable suspension of collagen particles (Piez, 1985)
Gynecological applications	Sponges (Chvapil, 1979)
Drug-delivery systems	Various forms (Stenzel *et al.*, 1974, Chvapil, 1979)

Courtesy R. Zenz

Glycosaminoglycans (GAG)

- Linear polysaccharides bound to proteins; form the ground substance in the extracellular space of connective tissue, cartilage, tendon and blood vessel walls.

  The entire branched macro-molecule is called a proteo-glycan (protein with GAG sidechains)



Courtesy R. Zenz

Copolymers of collagen and glycosaminoglycyans

- Analogs of ECM have been synthesized and have been studied as implants in a **Template function**.
  - Type I collagen – chondroitin sulfate copolymers for healing of full thickness skin wounds (powder and films):
    - Strongly reduced scar formation.
    - Formation of an almost physiological dermis.
  - Inducing peripheral nerve regeneration
  - Regeneration of knee meniscus (dog, horse)

Courtesy R. Zenz