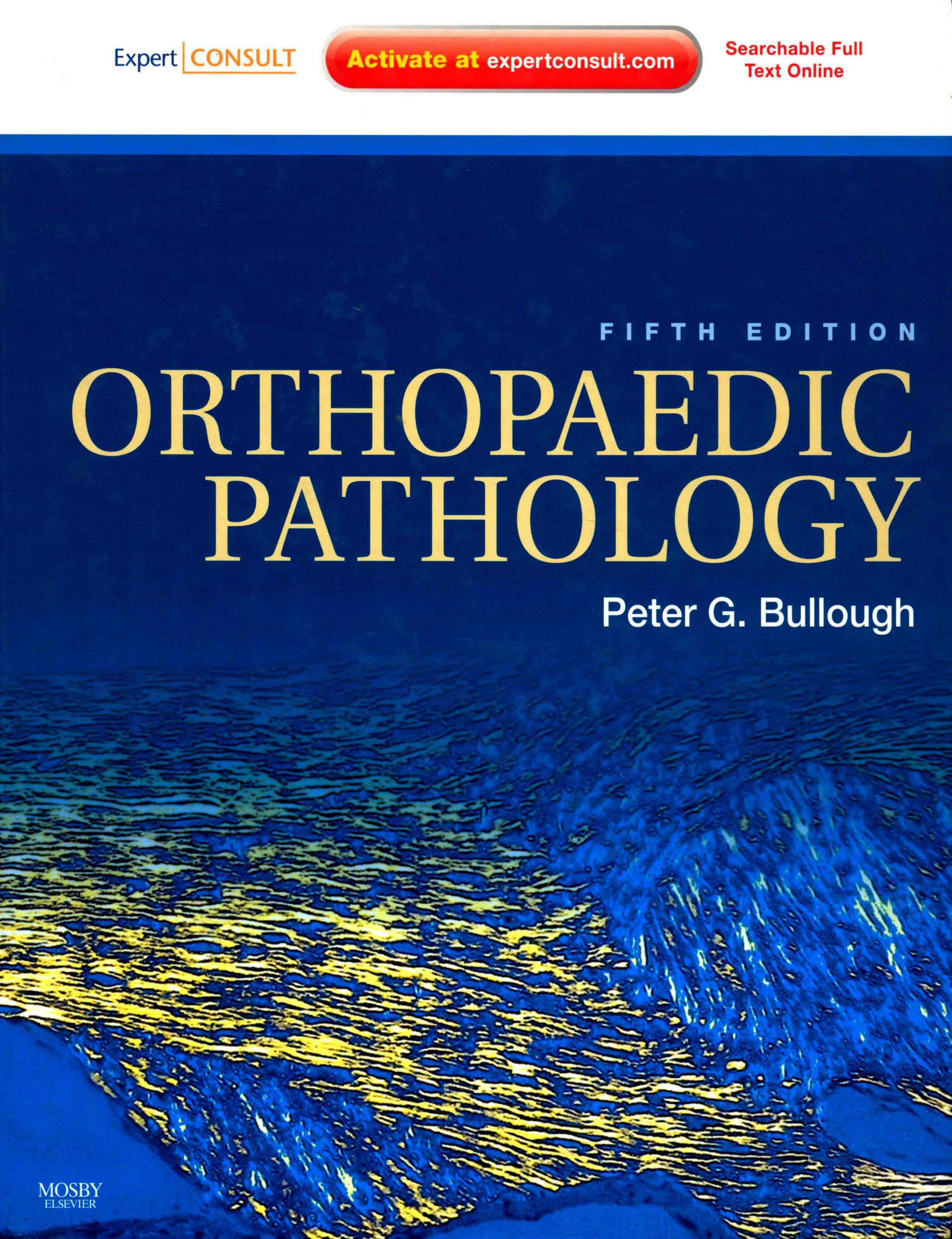
FIFTH EDITION

ORTHOPAEDIC PATHOLOGY

Peter G. Bullough



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Orthopaedic Pathology

Fifth Edition

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This work is dedicated to the memory of my Mother and Father,
and by the secretary of the New York Bone Club to its past and present members

Lauren V. Ackerman	1979 – 1993
Robert H. Freiberger	1979 – 2003
Andrew Huvos	1979 – 1996
Alex Norman	1979 – 2004
Hubert A. Sissons	1979 – 1990
Leon Sokoloff	1979 – 1999
German C. Steiner	1979 –
Si-Kwang (Sam) Liu	1980 – 2003
Aquilles Villacin	1980 –
Leonard B. Kahn	1980 –
Julius Smith	1981 – 1988
Howard D. Dorfman	1985 –
Michael J. Klein	1994 –
Harry Lumerman	1997 –
Nogah Haramati	2003 –
George Nomikos	2003 –
Benjamin Hoch	2003 –
Mark A. Edgar	2003 –

And many more, whose names on Earth are dark,
But whose transmitted effluence cannot die
So long as fire outlives the parent spark,

from *Adonais*
by Percy Bysshe Shelley (1792 – 1822)

Contributors

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Preface

I graduated from medical school in 1956. At that time, the standard texts in basic orthopaedics, physiology, pathology, and medicine provided little or no information with regard to the pathophysiology of bone and joint disease. Even as late as 1970 when I had the temerity to suggest to the Chief of the Trauma Service at a world famous medical school that perhaps we could learn something from studying bone biopsies from old ladies who had fractured their hips, my suggestion was met with incredulity. Today osteoporosis is recognized as one of the most serious problems facing the aging population.

Our own interest in, and understanding of, disease depends especially upon our teachers and colleagues. In this respect I was most fortunate in being accepted for a residency in anatomic pathology at the Beth Israel Hospital in Boston, where there was a strong tradition of intellectual exchange between the various hospitals and medical schools in the city. This was followed by a two-year fellowship at the Hospital for Joint Disease, New York, with Dr. Henry Jaffe whose whole life had been dedicated to orthopedic pathology in that great institution.

Four years spent in the department of Orthopedic Surgery at the University of Oxford exposed me to one of the most creative and imaginative orthopedic surgeons of his generation, Professor Jose Trueta, as well as two of the brightest young minds of British orthopedics at that time, Mr. Michael Freeman and Mr. John Goodfellow. In 1968 at the invitation of Dr. Philip Wilson Sr., I came to the Hospital for Special Surgery in New York City.

Much of the ever increasing sophistication in the diagnosis of bone and joint disease, I believe, we owe to the foundation in 1972 of the International Skeletal Society, which, for the first time, provided a wider venue for the discussion of the radiographic and histologic diagnosis of bone and joint disease. From its inception this society was interdisciplinary, drawing its members from the leading exponents of radiology, pathology, orthopaedics, and rheumatology in the Americas, Europe, Asia, and Australia. As a result of the annual meetings tremendous progress in diagnostic acumen has been achieved and disseminated through both very successful annual refresher courses offered by the society, and its journal – Skeletal Radiology.

The foundation in 1979 of a local New York Bone Club has provided a level of intellectual fellowship for which I am profoundly grateful. Our monthly meetings over the past 30 years have taught me more of my profession than I would have ever thought possible.

This text was first published in 1984 and was intended to provide a concise, yet lavishly illustrated and comprehensive introduction to the pathology of bone and joint disorders. The target audience was trainees in orthopaedics, radiology, and pathology. *Orthopaedic Pathology* was one of the early textbooks to be published in full color and this I believe helped to make an understanding of the subject under discussion much more accessible to those whose daily work did not involve the use of the microscope.

Using various imaging techniques, the radiologist may observe the virtual morbid anatomic changes associated with musculoskeletal disease. The histologist in his intent to interpret tissue sections is helped considerably by both clinical and radiologic correlation; without such correlation, serious mistakes are possible. With these thoughts in mind, in the illustration of the conditions under discussion, I have tried to make use of the various imaging techniques now available, and a splendid chapter, written for the nonspecialist by Professor Judith Adams and her colleague Dr. Sarah Jackson, on imaging techniques, interpretation, and strategies is included in the text.

Most of the gross photographs and photomicrographs used in the book were taken over the many years of my professional life. Many of the clinical radiographs are from the Radiology Department at the Hospital for Special Surgery, and I thank all the members of that department for their assistance especially Drs. Robert Freiberger, Robert Schneider, and Douglas Mintz. Additional illustrations have been generously contributed by numerous colleagues throughout the world, mostly members of the International Skeletal Society, to whom I am extremely grateful.

Line drawings have been used to indicate specific features in photographs, and where the three-dimensional or temporal aspects of a structure must be shown, color schematic drawings or anatomic drawings are provided.

The bibliography is arranged by chapter, and subdivided by disease. Nowadays the availability of the internet obviates the need for exhaustive bibliographies. So I have focused on including older references that have been useful to me and that may be less accessible via the internet.

In preparation of the first edition of this book, I was fortunate to have the assistance of Dr. Vincent Vigorita, who had just completed his fellowship at Memorial Hospital before joining our staff as assistant pathologist. For the second edition, I had the invaluable help of Dr. Rafael Castro. For this as well as the third and fourth editions, Dr. Philip Rusli, who has been with the pathology department for the past eighteen years, has been my amanuensis. With his organizational skills, he has managed the logistics of cataloging illustrations, checking references, tracking down radiographs, and many, many other tasks that are entailed in such a project as this. I am extremely grateful to him for all his help and support. Many of the images in this edition have benefitted from the expert Photoshop editing of Mr. Percy Addo-Yobo, a young Ghanese student lately working in our department.

I am indebted to my colleagues, the physicians, surgeons, and technical staff of the Pathology Department at the Hospital for Special Surgery – both past and present and especially Drs. Philip Wilson, Manjula Bansal, Edward DiCarlo, Adele Boskey, Stephen Doty, and Cathleen Raggio for their never failing support in this and other projects over the years. I am most grateful to Dr. Mark Edgar for his careful reading of the text, and his invaluable contributions and suggestions for its improvement. Finally, I thank my friends on the staff of Elsevier, especially William Schmitt and Andrea Vosburgh, for the care and hard work that went into the preparation of this book for publication.

Contents

SECTION I

Normal

CHAPTER 1

Normal Skeletal Structure and Development

First and foremost, bone, cartilage, ligaments, and tendons have a mechanical function: providing protection, movement, and stability. Unlike the parenchymal organs, which are composed mainly of cellular elements with a metabolic function, the connective tissues are mostly formed of an extracellular matrix that is formed of materials to resist the tensile and compressive forces to which they are subjected.

The microscopic examination of bone dates back to the earliest days of microscopy. In 1691, Clopton Havers published his *Osteologia Nova*, in which he described the pores in the cortical bone that we now refer to as haversian canals (Fig. 1-1). Since then, major contributions to the study of bone anatomy and histology have been made by many of the most famous names in medicine. In 1733, Cheselden published the *Osteographia*, which contained full and accurate descriptions of all human bones gained with the use of the camera obscura (Fig. 1-2), and in 1754, the beautiful and accurate work of Albinus on bone and muscle established a new standard in anatomic illustrations.

The experiments of Haller in 1763 contributed greatly to the understanding of bone formation, and in 1772, Hunter did much to elucidate the mechanism of bone growth, particularly its appositional growth rather than that of interstitial growth such as occurs in other organ systems (Fig. 1-3). Bichat, in the early 1800s, stressed the importance of the material tissue elements shared among the different organ systems (hence histology) and, in particular, described the synovial membrane. Virchow, the father of modern pathology, wrote classic descriptions of several bone tumors and metabolic disturbances (Fig. 1-4).

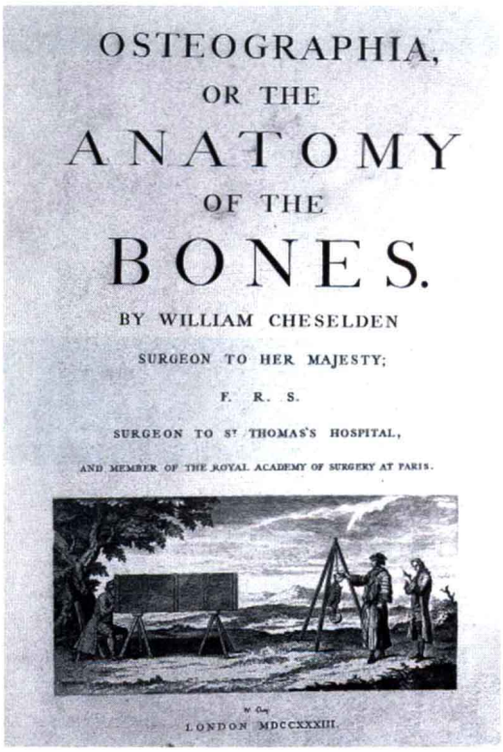
OSTEOGRAPHIA,
OR THE
ANATOMY
OF THE
BONES.
BY WILLIAM CHESELDEN
SURGEON TO HER MAJESTY;
F. R. S.
SURGEON TO ST THOMAS'S HOSPITAL,
AND MEMBER OF THE ROYAL ACADEMY OF SURGERY AT PARIS.
LONDON MDCCXXXIII.

FIGURE 1-2 William Cheselden, 1688–1752. In 1733 he published the *Osteographia*, the first full and accurate description of the anatomy of the human skeletal system. (Title page of Cheselden W: Osteographia, or the Anatomy of the Bones. W. Boyer, London, 1733. From the Wellcome Library, London.)

Matrix

Some knowledge of the matrix constituents is essential to the understanding of connective tissue diseases. The various types of collagen account for 70% of all body proteins and are the principal extracellular constituents of connective tissue (Table 1-1). Type I collagen is the most common form of collagen and the major collagen found in skin, fascia, tendon, and bone. Type I collagen is made up of bundles of fibrils, which, in turn, are composed of stacked molecules formed from polypeptide chains arranged in a triple

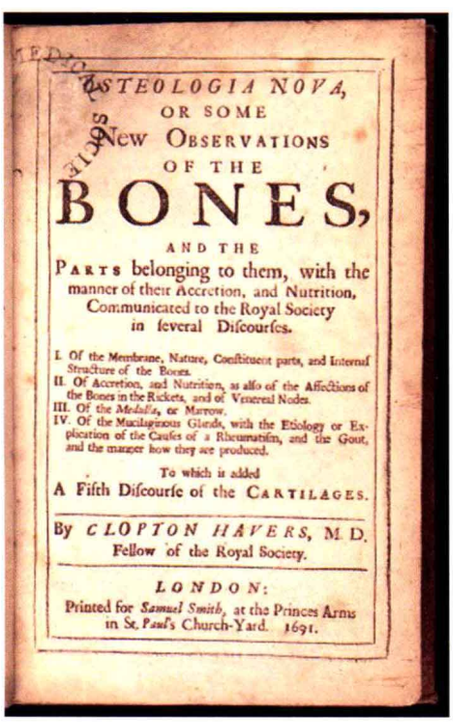
OSTEOLOGIA NOVA,
OR SOME
New Observations
OF THE
BONES,
AND THE
Parts belonging to them, with the manner of their Accretion, and Nutrition, Communicated to the Royal Society in several Discourses.
I. Of the Membrane, Nature, Constituent parts, and Internal Structure of the Bones.
II. Of Accretion, and Nutrition, as also of the Affections of the Bones in the Rickets, and of Venereal Nodes.
III. Of the *Medulla*, or Marrow.
IV. Of the Mucilaginous Glands, with the Etiology or Explication of the Causes of a Rheumatism, and the Gout, and the manner how they are produced.
To which is added
A Fifth Discourse of the Cartilages.
By *CLOPTON HAVERS*, M. D.
Fellow of the Royal Society.
LONDON:
Printed for *Samuel Smith*, at the Princes Arms in St. *Paul's* Church-Yard. 1691.

FIGURE 1-1 Clopton Havers, 1657–1702. The first description of haversian canals and Sharpey's fibers. (Title page of Havers C: Osteologia Nova. Printed for Samuel Smith, London, 1691. From the Wellcome Library, London.)

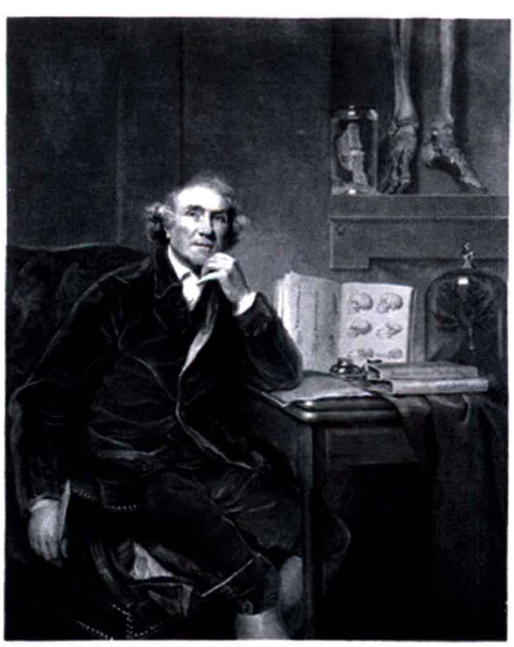

FIGURE 1-3 John Hunter, 1728–1793. 'To know the effects of disease is to know very little; to know the cause of the effects is the important thing.'

FIGURE 1-4 Rudolf Virchow, 1821–1902. In defining disease as the cells' reaction to an altered environment, Virchow set the stage for modern medicine. He was not only a great doctor but also a great liberal politician and philosopher. (Photograph by J.C. Schaarwächter, 1891. From the Wellcome Library, London.)

helical pattern (Figs. 1-5 and 1-6). At least 29 distinct types of collagen composed of at least 43 genetically distinct chains are now known, and these types vary both in size and configuration. Some contain interrupted helical structures aligned in a staggered array to form fibrils. There are also nonfiber-forming collagens, which have varying functions such as binding sites for other matrix components (type IX) or the regulation of vascularization (type X) or fiber size (type XI) (Fig. 1-7).

Hyaline cartilage has a unique type of collagen, type II, which is structurally characterized by three identical triple helical α-1(II) chains. The type II fibrillar network, which will be discussed in more detail later, is essential both for maintaining the tissue's volume and shape as well as providing articular cartilage with its tensile strength when subjected to compressive loads.

Collagen synthesis is complex and includes both intracellular and extracellular events. During the processes of transcription and translation of the collagen genes, it is necessary that a number of intervening sequences (known as introns) are spliced out. Defects in this processing of bone type I collagen lead to either defective collagen chains or reduced amounts of collagen and the clinical disease of osteogenesis imperfecta.

The protein α-chains formed first are made up of sequences of amino acids of which glycine occupies every third position; the intervening positions are frequently occupied by either proline or lysine, which are later hydroxylated in preparation for the formation of the triple helix. (Proline and lysine hydroxylases require the presence of ascorbic acid, α-ketoglutarate, Fe^{++} and O_2. In the absence of vitamin C, collagen cannot be synthesized.)

TABLE 1-1 All Collagens

Type	Genes	Structure	Representative Tissues	Disorders
I	COL1A1, A2	Fibrils	Skin, bone, tendon, dentin, etc.	Osteogenesis imperfecta, Ehlers-Danlos syndrome
II	COL2A1	Fibrils	Hyaline cartilage, vitreous body	Collagenopathy, types II and XI, spondyloepiphyseal dysplasia (SED)
III	COL3A1	Fibrils	Skin, vessels	Ehlers-Danlos syndrome (EDS)
IV	COL4A1, A2, A3, A4, A5, A6	Meshwork	Basement membranes	Alport's syndrome, porencephaly, Goodpasture's syndrome
V	COL5A1, A2, A3	Fibrils	Hamster lung cell cultures, fetal membranes, skin, bone, placenta, synovial membranes	Ehlers-Danlos syndrome (classic type)
VI	COL6A1, A2, A3	Short chain	Vessels, skin, intervertebral disc, placenta, heart	Ulrich myopathy, Bethlem myopathy
VII	COL7A1	Long chain	Dermo-epidermal junction	EDS, epidermolysis bullosa
VIII	COL8A1, A2	Short chain	Descemet membrane, endothelial cells	Corneal dystrophies
IX	COL9A1, A2, A3	Short chain	Cartilage specific hyaline cartilage, vitreous humor	Multiple epiphyseal dysplasia, Stickler syndrome
X	COL10A1	Short chain	Cartilage specific growth plate (hypertrophic cartilage)	Schmidt's metaphyseal dysplasia
XI	COL11A1, A2	Fibrils	Hyaline cartilage	Collagenopathy, types II and XI, Stickler syndrome
XII	COL12A1	?	Embryonic skin and tendon, periodontal ligament	?
XIII	COL13A1	Short chain	Endothelial cells, fibroblast, blood vessels	?
XIV	COL14A1	Glycoprotein	Fetal skin and tendon	?
XV	COL15A1	Interrupted collagen	Embryonic organs	?
XVI	COL16A1	FACIT	?	?

(Continued)

TABLE 1-1 All Collagens—cont'd

Type	Genes	Structure	Representative Tissues	Disorders
XVII	COL17A1	Transmembrane	Basement membrane	Epidermolysis bullosa
XVIII	COL18A1	Multiplexin	Vasculature	Knobloch's syndrome
XIX	COL19A1	FACIT		
XX	COL20A1	Short chain	Cornea	
XXI	COL21A1	FACIT	Skeletal muscle and heart	
XXII	COL22A1	FACIT	Tissue junctions	
XXIII	COL23A1	Transmembrane	?	?
XXIV	COL24A1	?	Bone, retina	(Marks embryonic bone formation)
XXV	COL25A1	Fibril	Brain specific	Alzheimer amyloid plaque component (senile Alzheimer's disease)
XXVI	COL26A1	Multiplexin	Uterus	?
XXVII	COL27A1	Fibril	Brain, lung	
XXVIII	COL28A1	FACIT	Lung	
XXIX	COL29A1	FACIT	Skin, lung	

FACIT, Fibril-associated collagens with interrupted triple-helix.

The fiber-forming collagens are well suited to resist the effect of pulling, that is, tension; thus the matrix of tendons and ligaments is mainly type I collagen. However, the fiber-forming collagens do not resist bending or compression well, and because the matrices of both bone and cartilage are subjected to these latter types of forces, they contain stiffening substances. In bone, the stiffening substance takes the form of a microcrystalline analog of geologic hydroxyapatite: $Ca_{10}(PO_4)_6(OH)_2$ (Fig. 1-8). (The crystals in mineralized bone are too small to be seen by light microscopy, being approximately only $2 \times 2 \times 25$ nm in size, but they can be visualized by electron and atomic force microscopy.) The apatite crystals provide strength in compression, although, as would be expected, they are weak in bending and tension.

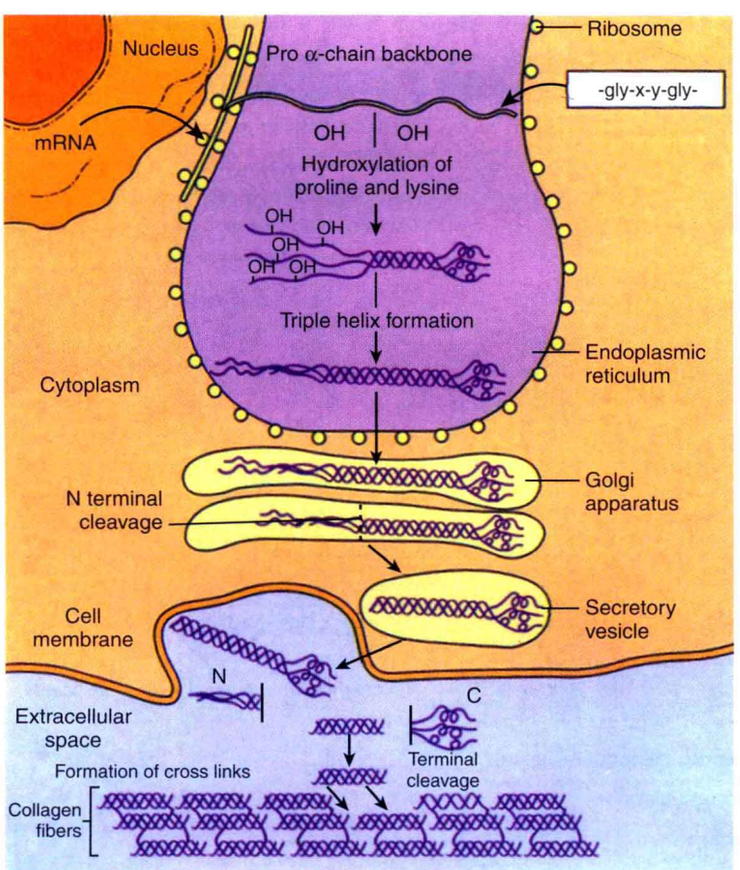

FIGURE 1-5 Schematic diagram of intra- and extracellular collagen synthesis. In the pro-α-chain, glycine occupies every third position. Commonly, -x- and -y- are lysine and proline. Cleavage of the N and C terminal fragments is an essential step in collagen fiber formation.

During development and aging, the relative mineral content of the bone increases, whereas the water content decreases. The perfection and size of the hydroxyapatite crystals in the bone also increases with age. (In addition to its mechanical functions the mineral also has a primary role to play in calcium homeostasis [see Chapter 8].)

In articular cartilage, the filler between the collagen fibers is composed of large, negatively charged macromolecules, the proteoglycans (PGs) (Fig. 1-9). These are a group of heterogenous molecules consisting of protein chains and attached carbohydrates that have a sticky gel-like quality. The major PG in cartilage is aggrecan, which contains a protein core that has a molecular weight (Mr) of approximately 215,000 and to which carbohydrate side chains (keratan and chondroitin sulfate) are attached. The aggrecan molecules interact with hyaluronan and this interaction is stabilized by link protein (Fig. 1-10). As many as 200 individual aggrecan molecules (subunits) bind to one hyaluronic acid chain (Mr $1\text{-}2 \times 10^6$) to form a giant aggregate (Mr 5×10^7 to 5×10^8).

PGs are highly charged molecules, often attached to collagen fibrils, which bind water, and this water accounts for approximately 70% of the wet cartilage tissue mass (Fig. 1-11). PGs in solution can expand to 50% of their volume. However, within hydrated cartilage the expansion of the PGs is restricted by the collagen network to approximately 20% of the maximum possible. The swelling (hydrolic) pressure thus created within the cartilage resists applied compressive loads.

When cartilage is loaded, some water is extruded; removal of the load permits the imbibing into the tissue of more water, together with essential nutrients, until the swelling pressure of the PGs is again balanced by the resistance of the collagen network.

The aggrecan shows an age-related decrease in size and enrichment in keratan sulfate relative to chondroitin sulfate. Associated with these changes is cartilage dehydration.

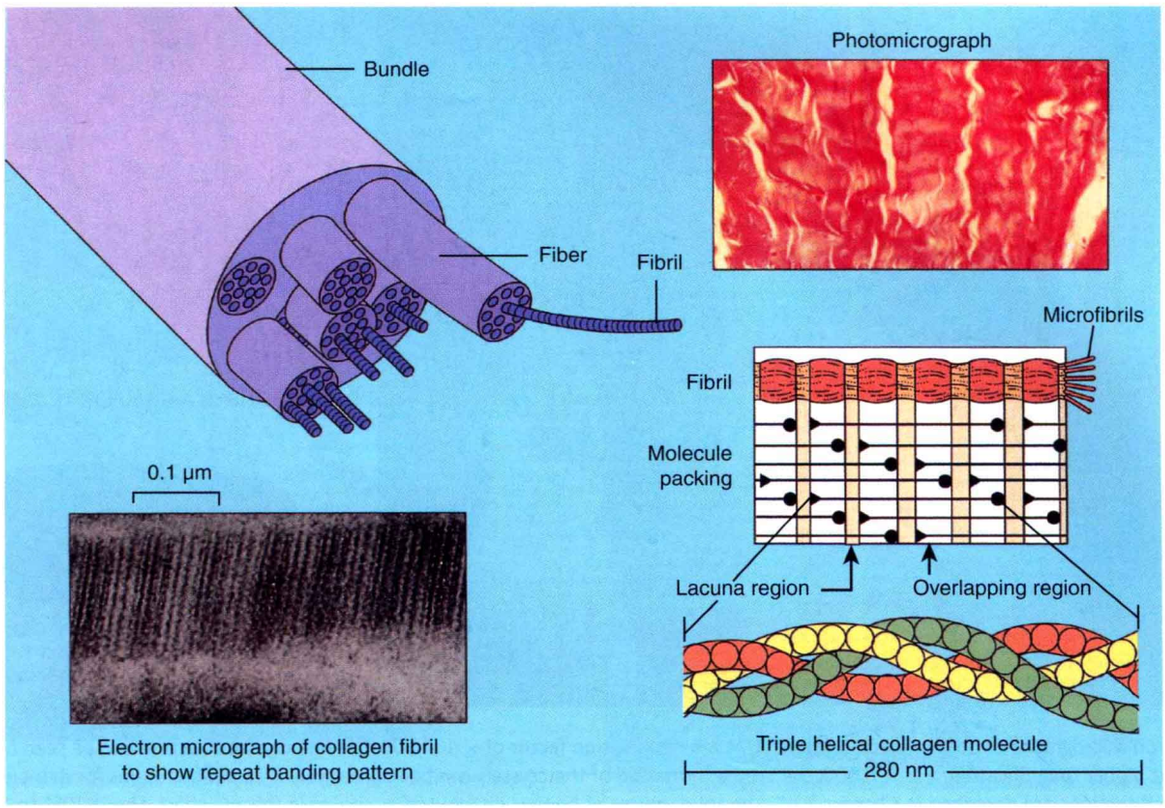

FIGURE 1-6 Collagen structure. On microscopic examination of ligamentous tissue, stained with H&E, the wavy homogenous strands of pink material represent bundles of type I collagen fibers. The collagen molecule is a triple helix formed of polypeptide chains, which in turn are formed of repeating tripeptide sequences of glycine-x-y-glycine-x-y, etc., in which x and y are frequently proline and lysine. Visualized by transmission electron microscopy, the individual collagen fibrils are seen to have regular light and dark bands. As can be seen from the drawing, the bands result from the gaps between the individual molecules of collagen, which then overlap the adjacent molecules.

In addition to aggrecan, cartilage contains smaller PGs that contain dermatan sulfate (e.g., biglycan, decorin, fibromodulin, lumican). These PGs are present in lower concentrations than aggrecan, they bind growth factors and thus play a role in tissue metabolism and may also have a role in preventing joint adhesions. In older individuals, they show increasing concentration, especially in the superficial layers.

Articular cartilage also contains other extracellular noncollagenous proteins. Anchorin is a protein on the surface of chondrocytes involved in binding of these cells to extracellular matrix components, possibly transmitting information on matrix loading to chondrocytes. Fibronectin, thrombomodulin, thrombospondin, cartilage oligomeric matrix protein, cartilage-associated protein are found in cartilage,

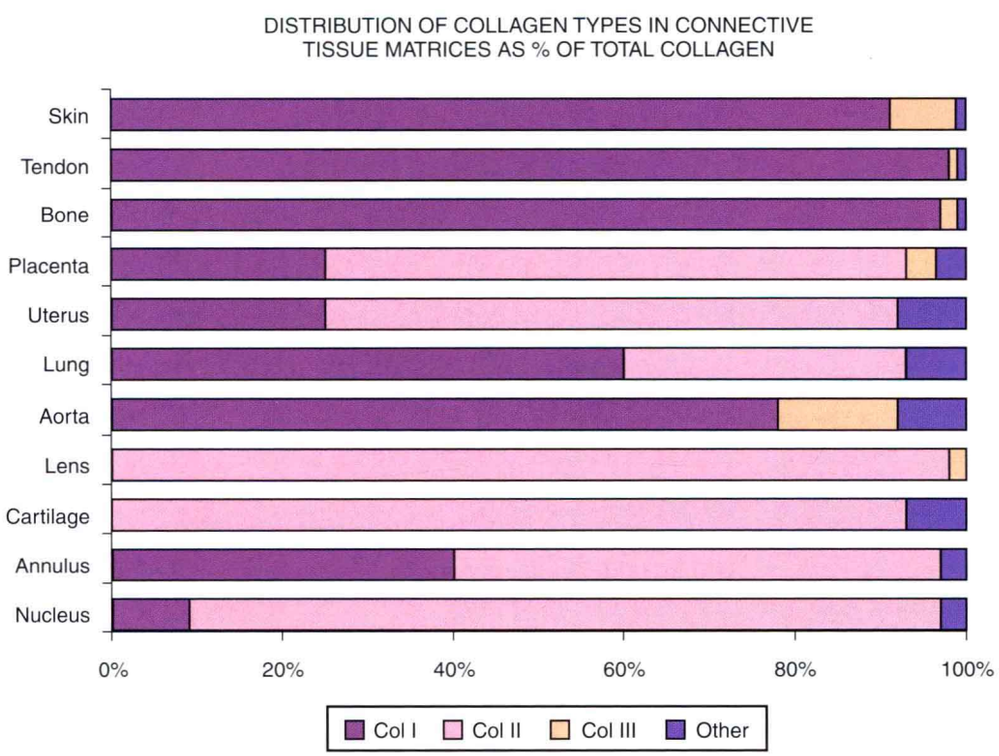

FIGURE 1-7 The distribution of the most common collagens in various tissues.

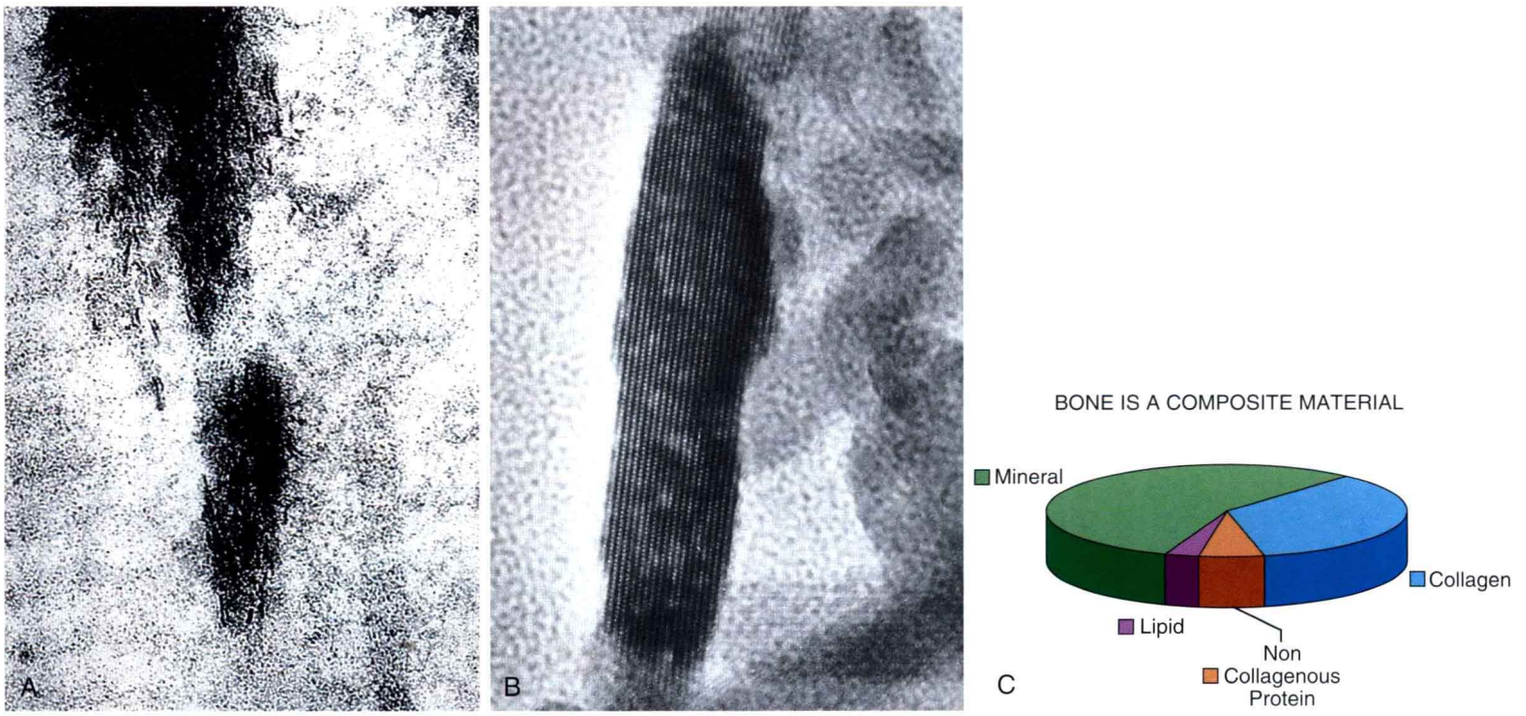

FIGURE 1-8 Electron micrographs of bone mineral crystals. **A**, At a magnification factor of × 101,500, the fine crystal structure can be seen overlying the collagen fibrils. **B**, At higher magnification, × 2,110,000, the lattice formation of the crystals can be appreciated. (The various stains for demonstrating calcium salts in undecalcified sections are described in Chapter 2.) **C**, The solid matter of bone is distributed as shown in this pie chart. About 10% to 11% of total bone mass is attributable to water.

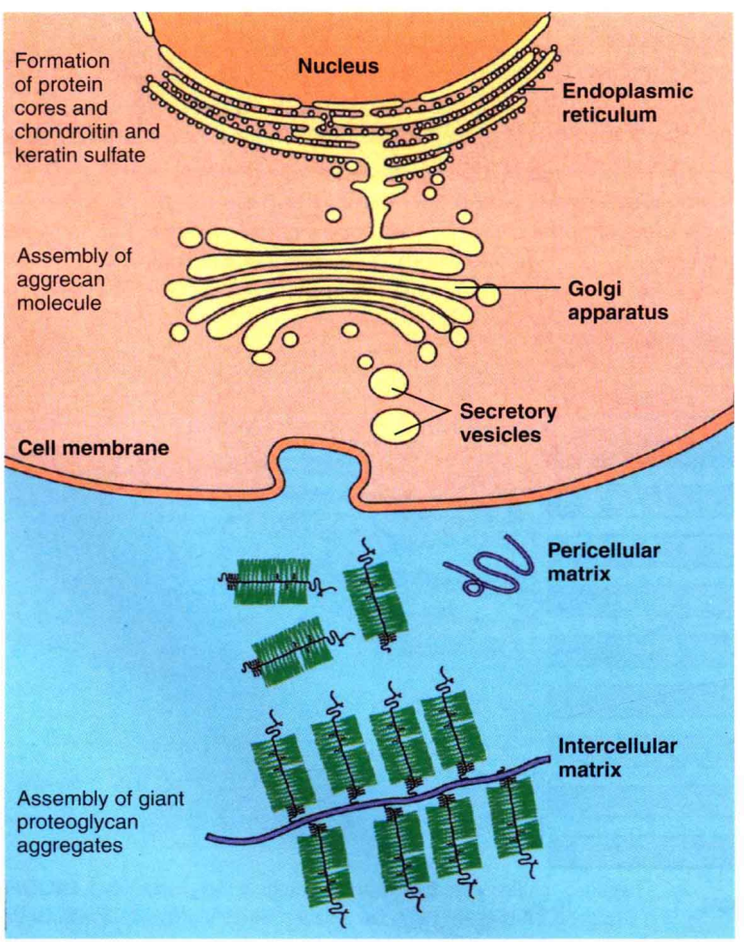

FIGURE 1-9 Schematic representation of proteoglycan synthesis.

but their precise functions are not yet known. The possible arrangement of some of these components within the cartilage matrix is shown schematically in Figure 1-12.

The matrix components of the connective tissues are manufactured as well as regulated by cells that themselves occupy only a small volume of the tissues. Nevertheless, these cells, that is, fibroblasts (cells that produce fibrous tissue, including ligaments and tendons), osteoblasts (cells that produce bone), and chondroblasts (cells that

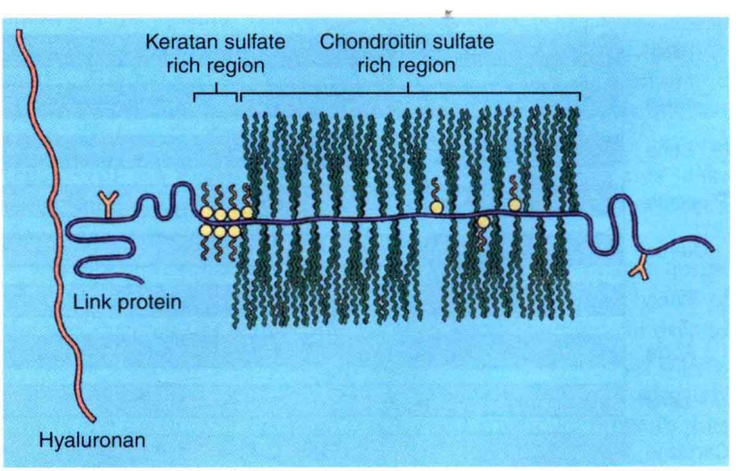

FIGURE 1-10 Structure of aggrecan. The proteoglycan (PG) aggrecan is made up of a polypeptide chain interspersed with extended regions, to which are attached sulfated glycosaminoglycan side chains (keratan sulfate and chondroitin sulfate). The PG aggrecan associates with hyaluronic acid in association with link protein. Up to 200 aggrecan molecules can associate with hyaluronic acid to form a large molecular aggregate that is highly charged, and pulls water into the tissue.