Bone, Fracture, and Genetics

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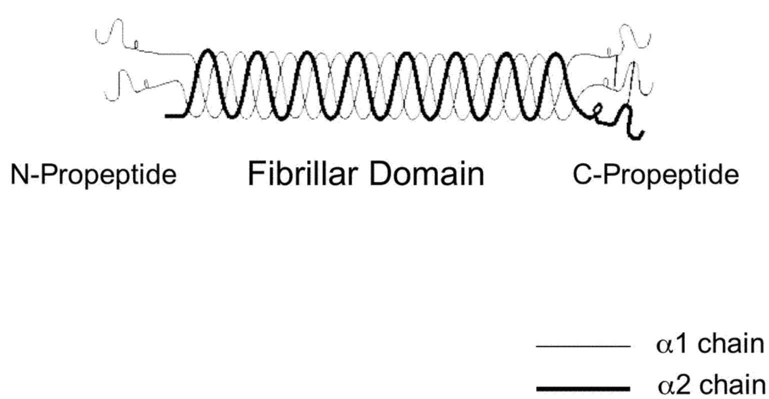
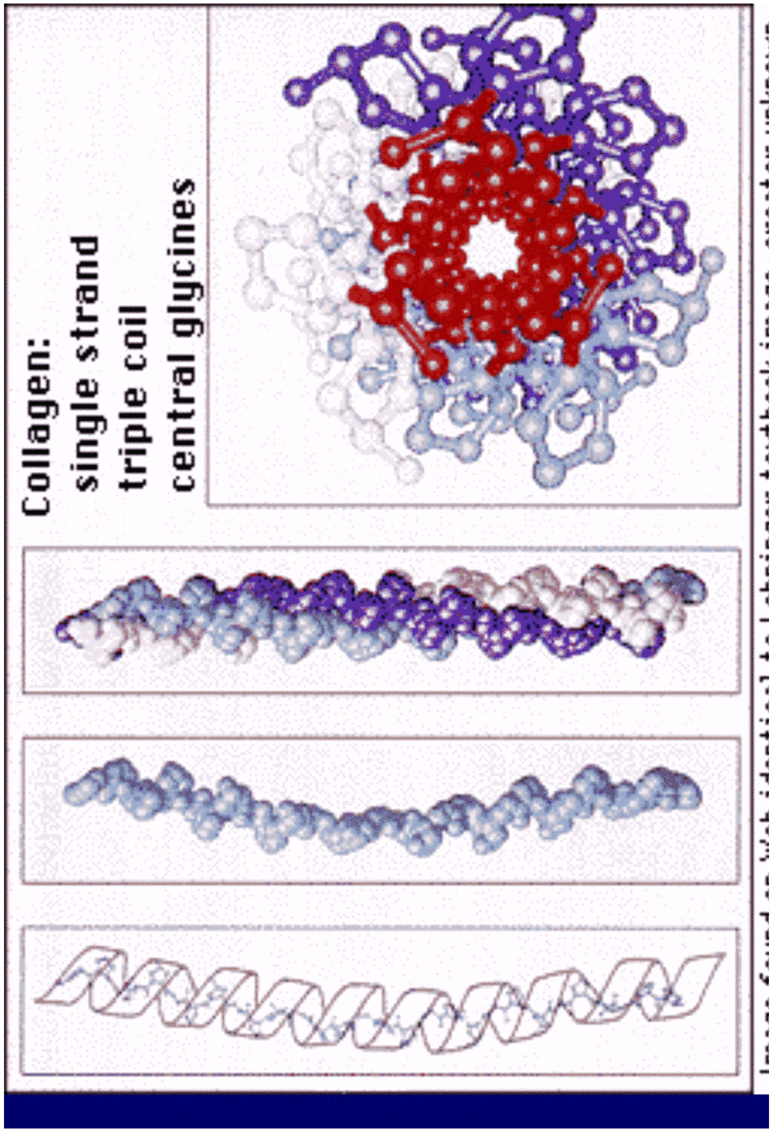
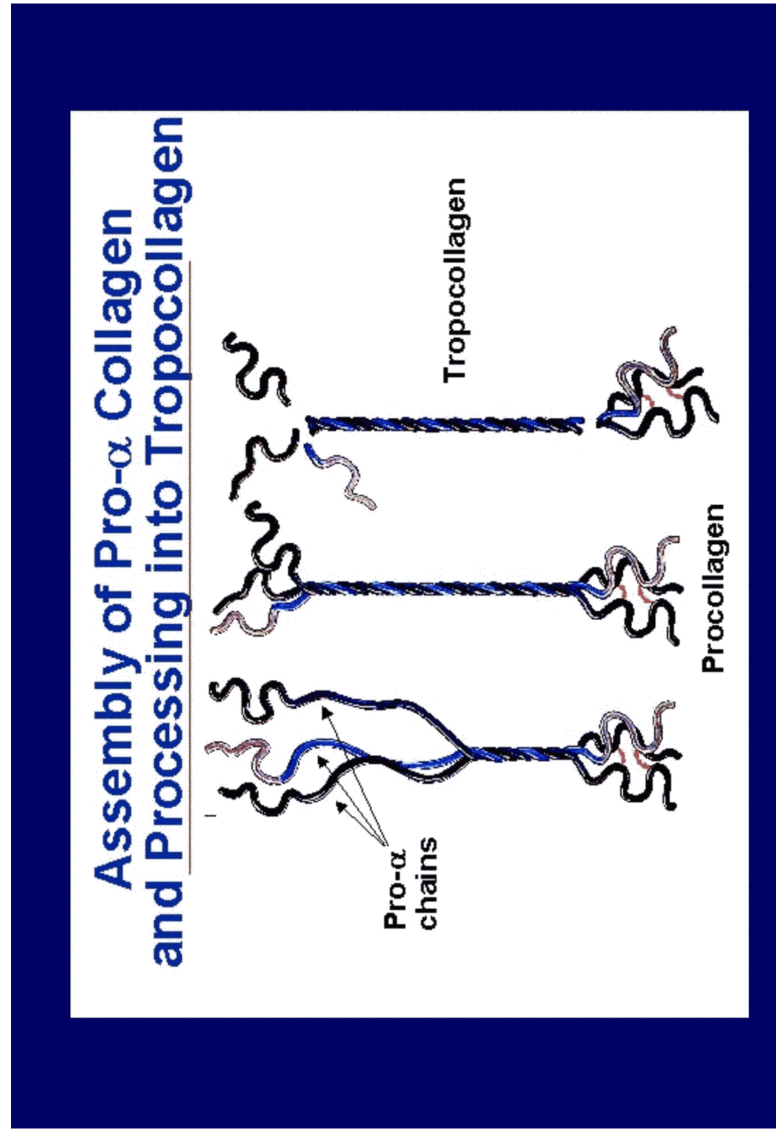
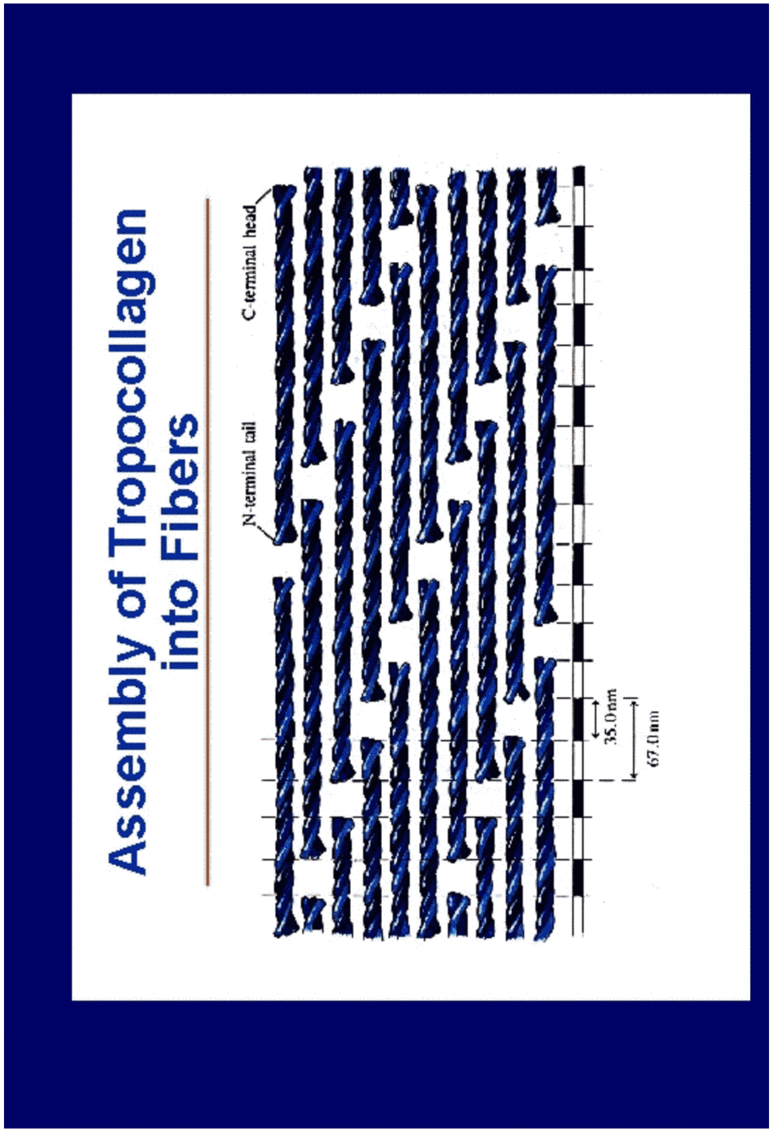
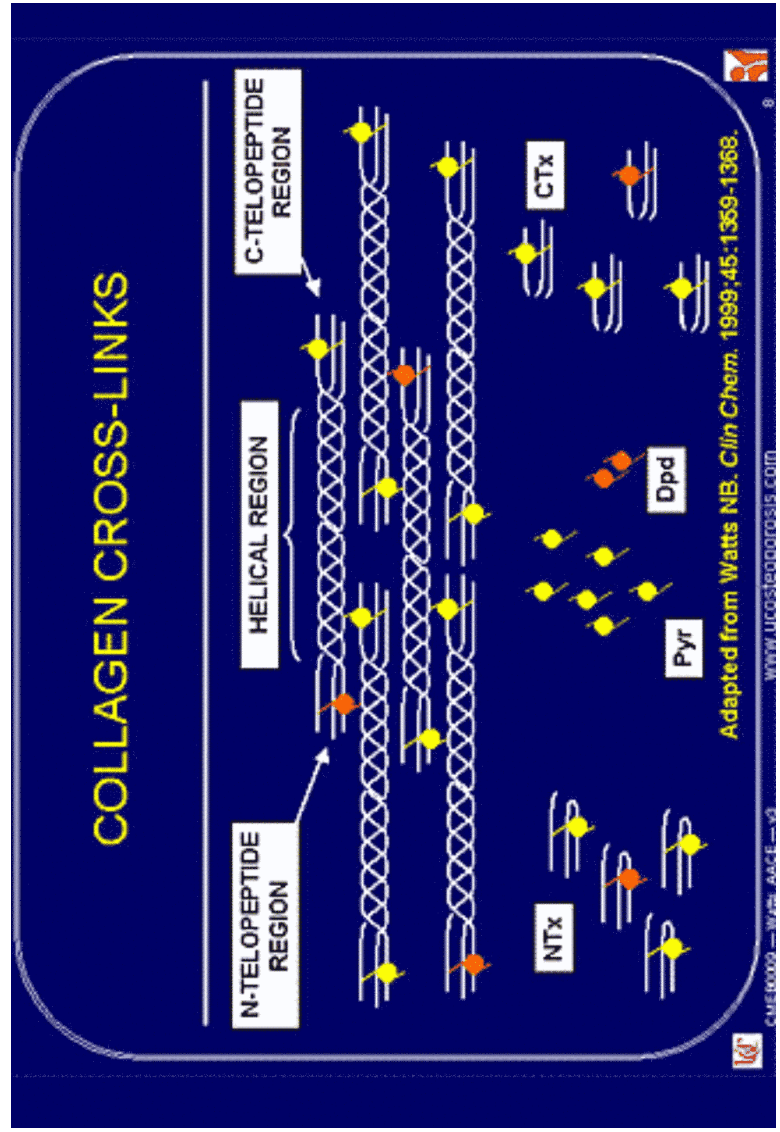
Procollagen Structure

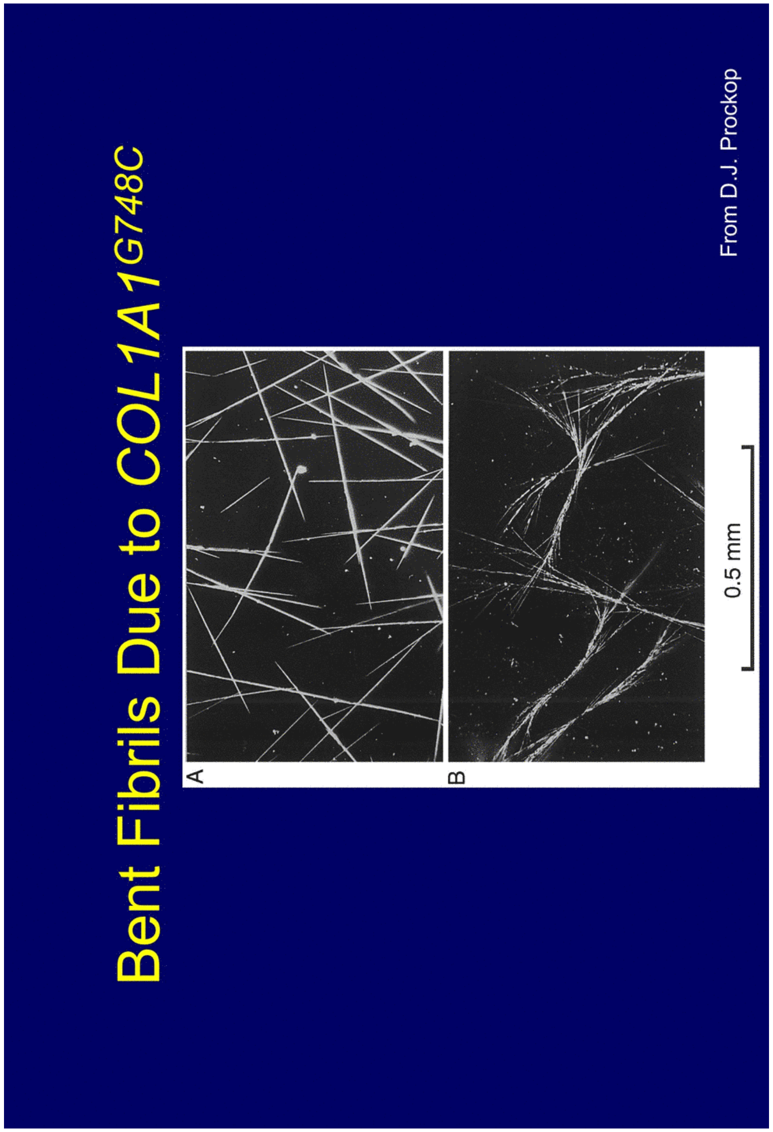


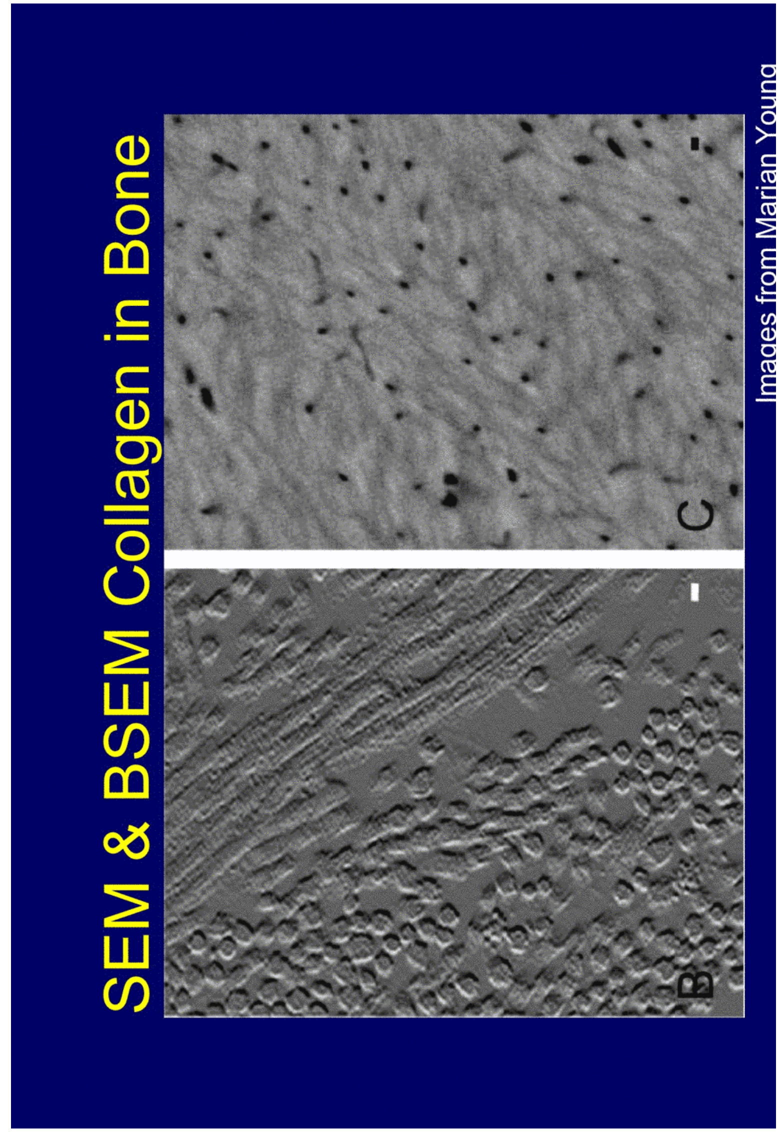

Collagen:
single strand
triple coil
central glycines


Assembly of Pro-α Collagen and Processing into Tropocollagen
Pro-α chains
Procollagen
Tropocollagen

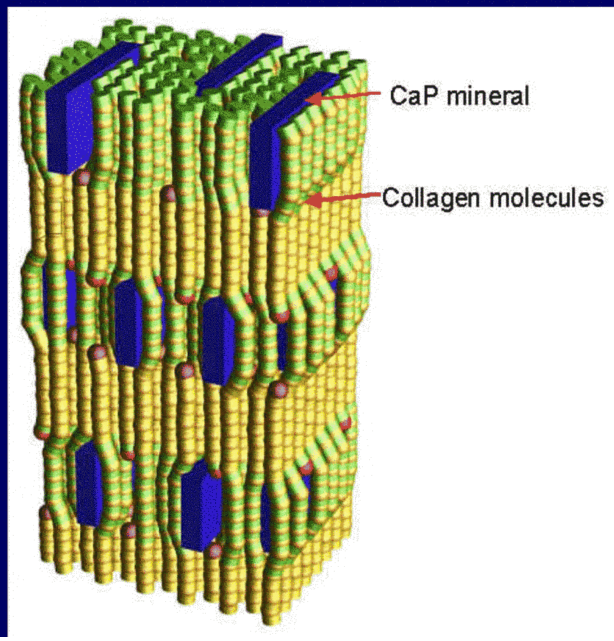

Assembly of Tropocollagen into Fibers
C-terminal head
N-terminal tail
35.0nm
67.0nm


COLLAGEN CROSS-LINKS
C-TELOPEPTIDE REGION
HELICAL REGION
N-TELOPEPTIDE REGION
CTx
Dpd
Pyr
NTx
Adapted from Watts NB. Clin Chem. 1999;45:1359-1368.


Bent Fibrils Due to *COL1A1*^{G748C}
A
B
0.5 mm
From D.J. Prockop


SEM & BSEM Collagen in Bone
B
C
Images from Marian Young

Intercalated Apatite



Chu, Hsiao, Burger, Glimcher

Bone Functions

- Metabolic- reservoir of exchangeable Ca and PO_4
- Mechanical- protection of vital structures and movement
- Fractures, especially those occurring with minimal trauma, are a major health problem

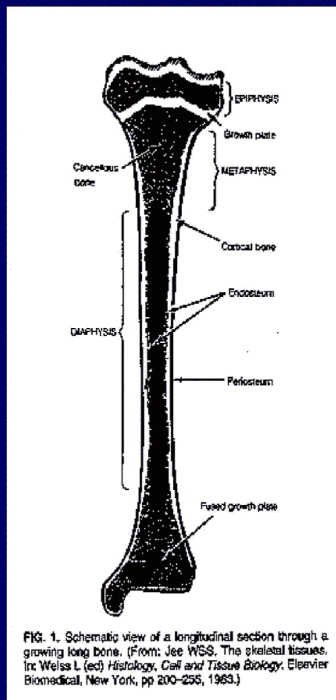


FIG. 1. Schematic view of a longitudinal section through a growing long bone. (From: Jee WSS. The skeletal tissues. In: Weiss L (ed) *Histology, Cell and Tissue Biology*. Elsevier Biomedical, New York, pp 200–255, 1983.)

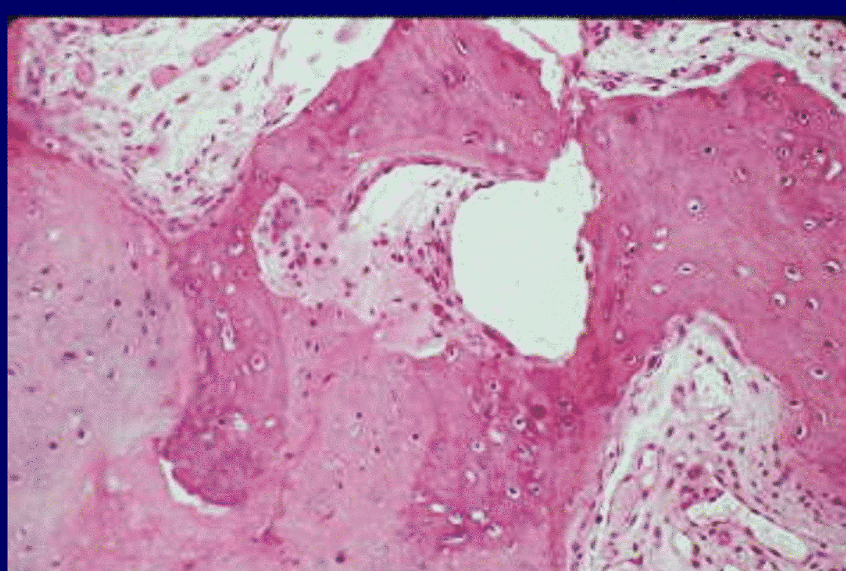
Bone Components

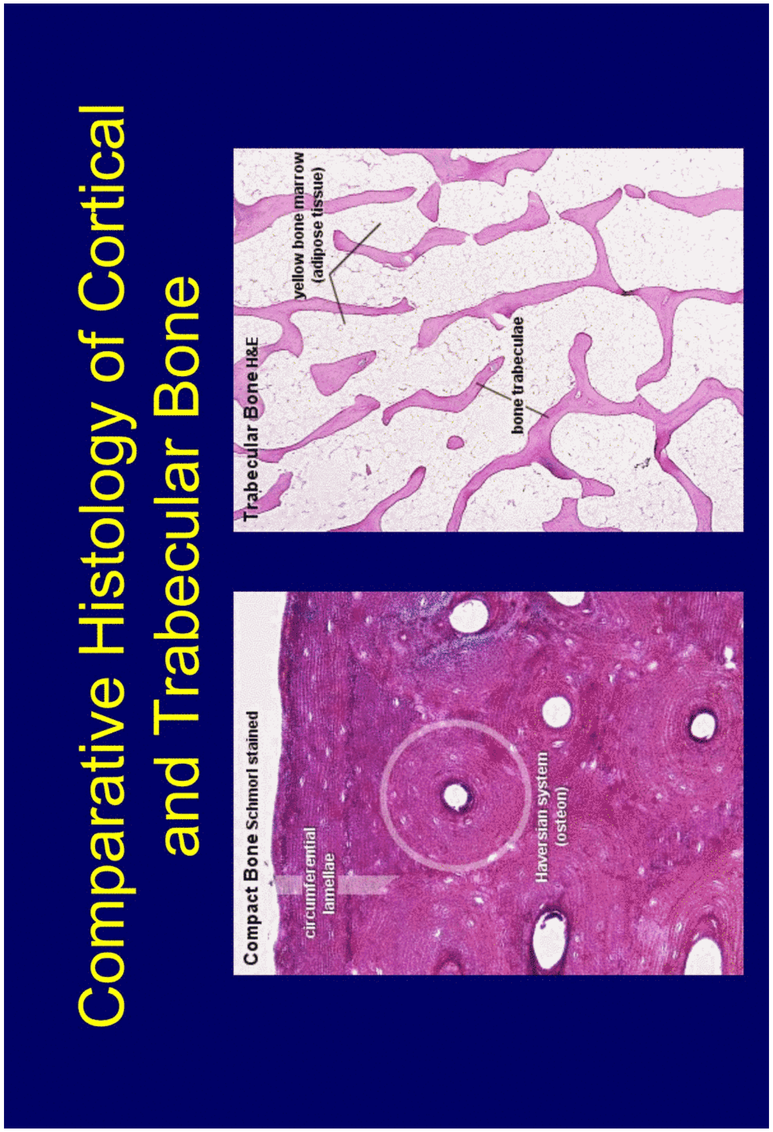
Cortical and trabecular bone are constituted of the same cells and the same matrix elements, but there are structural and functional differences.

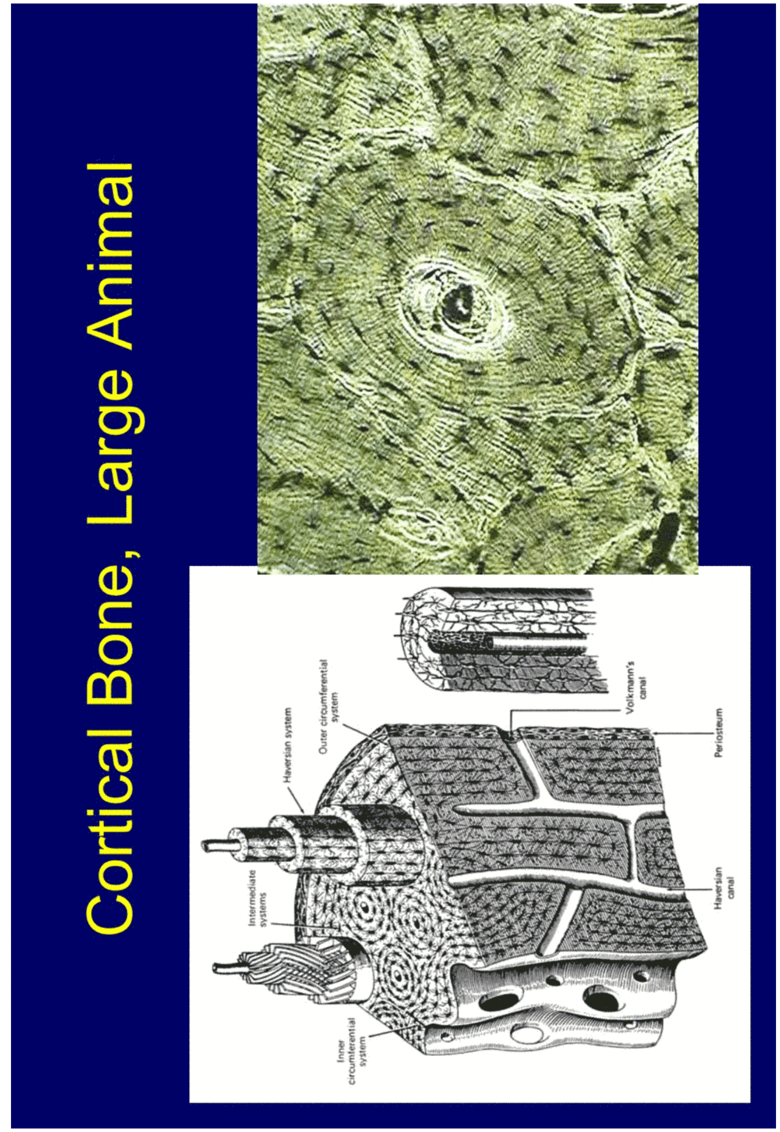
Cortical Bone
- 80-90% of volume is calcified
- Fulfills mainly a mechanical and protective function
- Always found on outside of bones and surrounds trabecular bone
- ~80% of bone

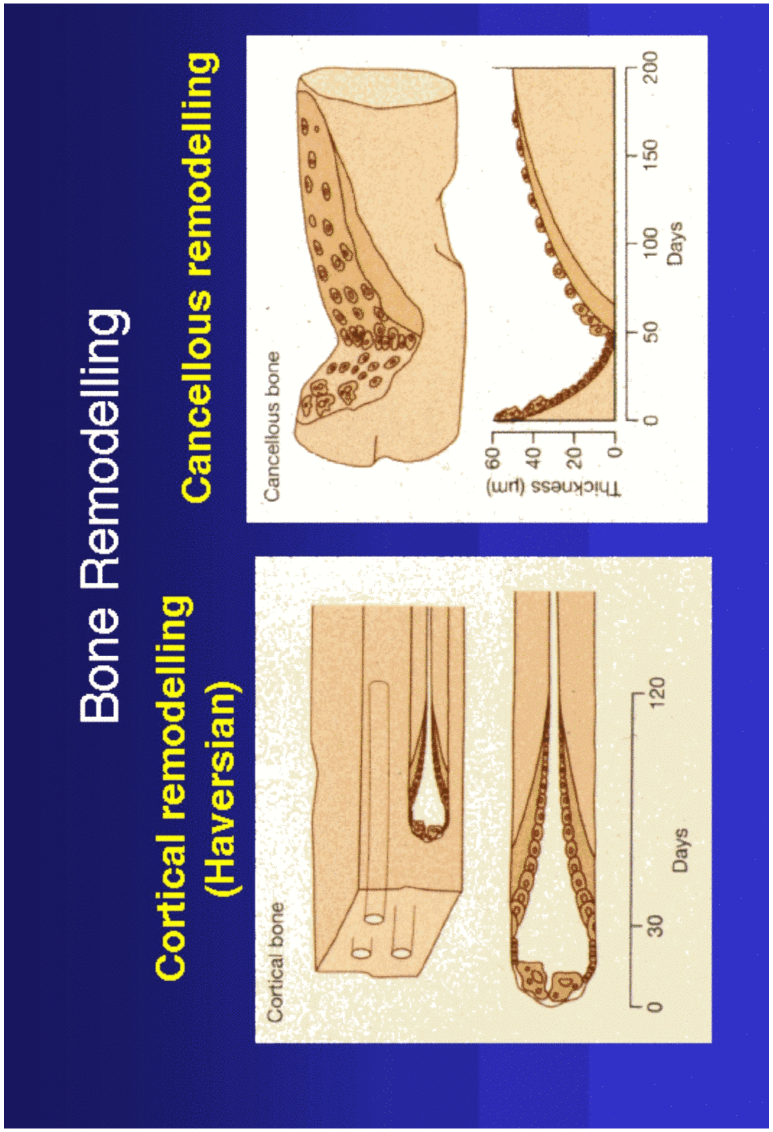
Trabecular Bone
- 15-25% of volume is calcified
- Fulfills mainly a metabolic function
- ~20% of bone

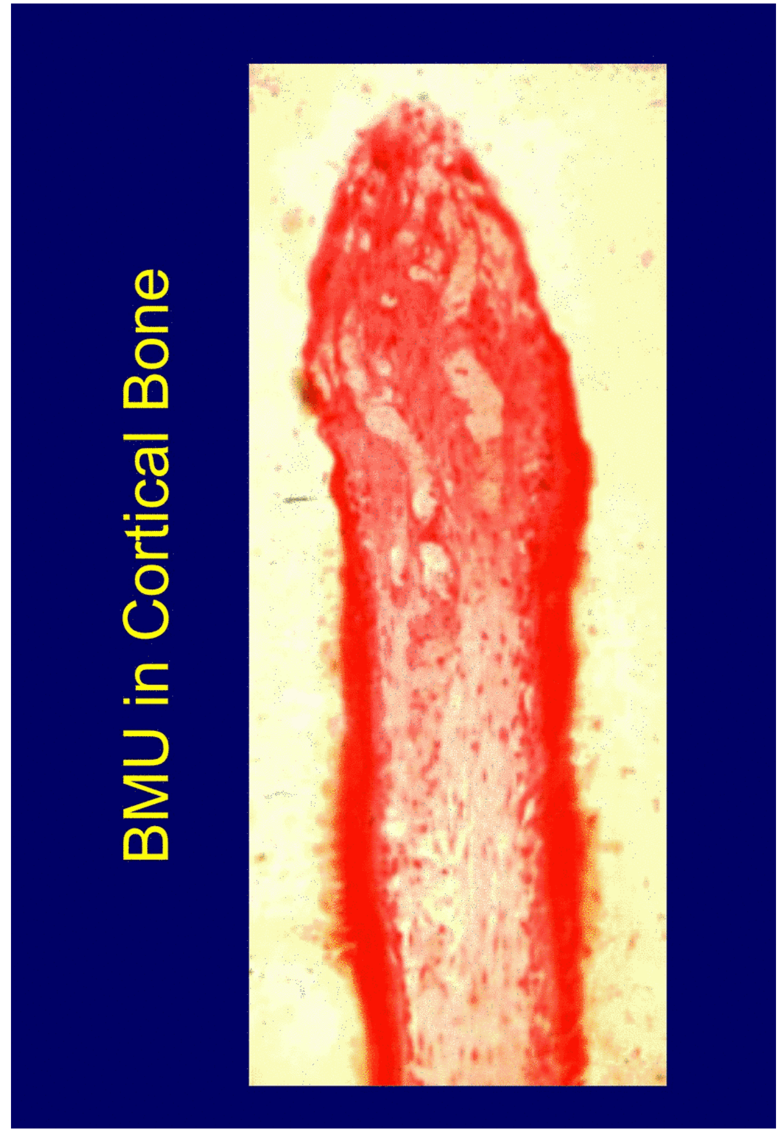
Woven Bone, Healing Fx

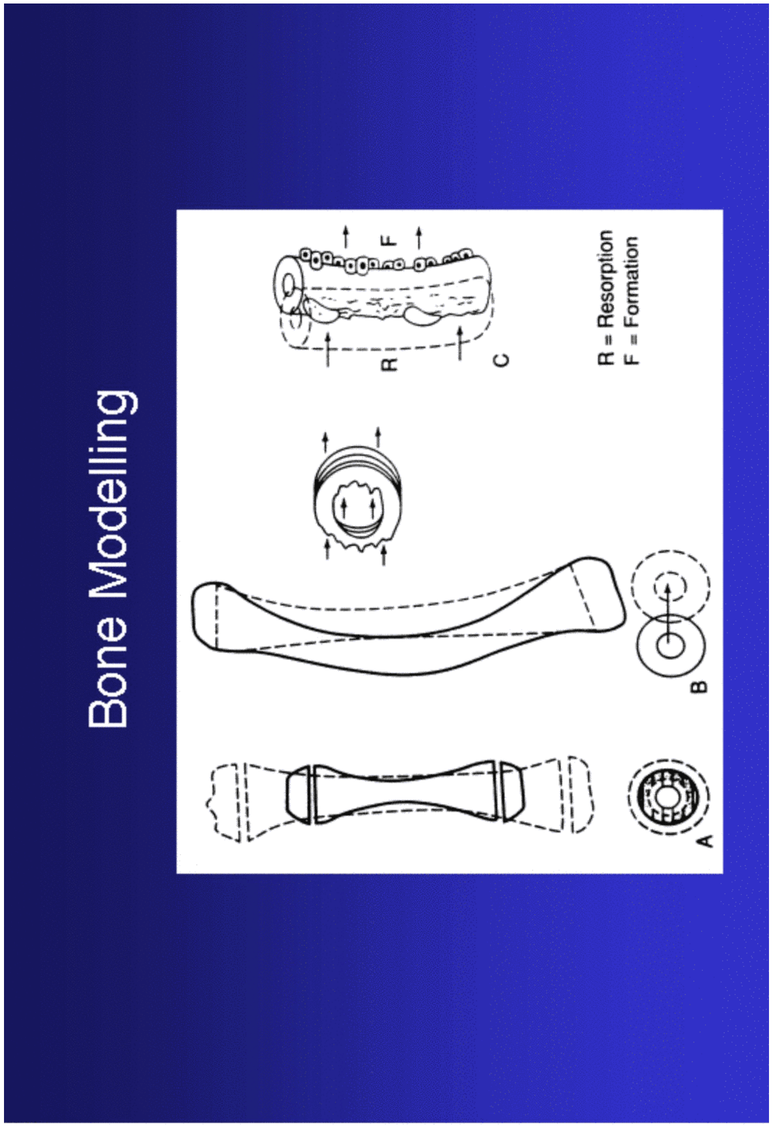


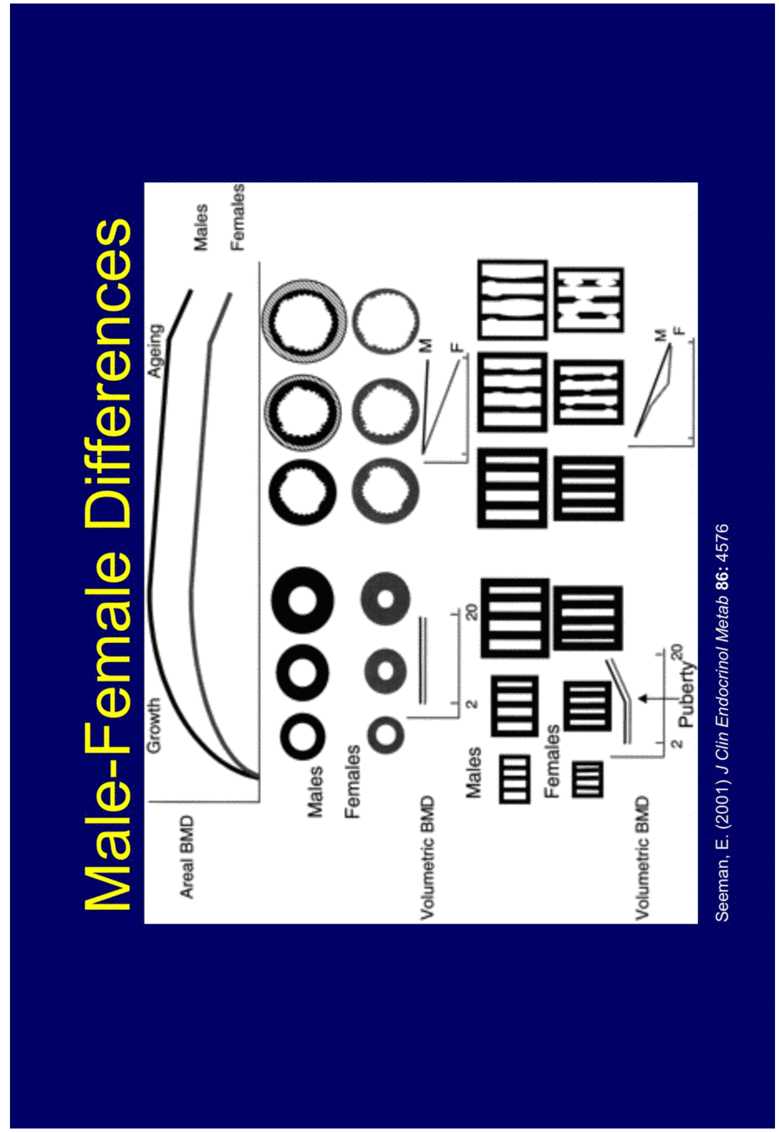

Comparative Histology of Cortical and Trabecular Bone
Compact Bone Schmorl stained
circumferential lamellae
Haversian system (osteon)
Trabecular Bone H&E
yellow bone marrow (adipose tissue)
bone trabeculae


Cortical Bone, Large Animal
Outer circumferential system
Haversian system
Volkmann's canal
Periosteum
Haversian canal
Intermediate systems
Inner circumferential system


Bone Remodelling
Cortical remodelling
(Haversian)
Cancellous remodelling
Cortical bone
0
30
Days
120
Cancellous bone
Thickness (µm)
60
40
20
0
0
50
100
150
200
Days


BMU in Cortical Bone

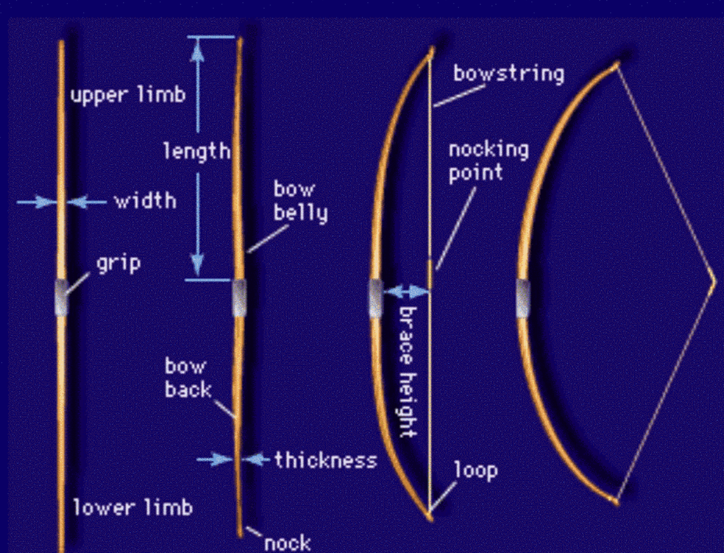

Bone Modelling
A
B
C
R
F
R = Resorption
F = Formation

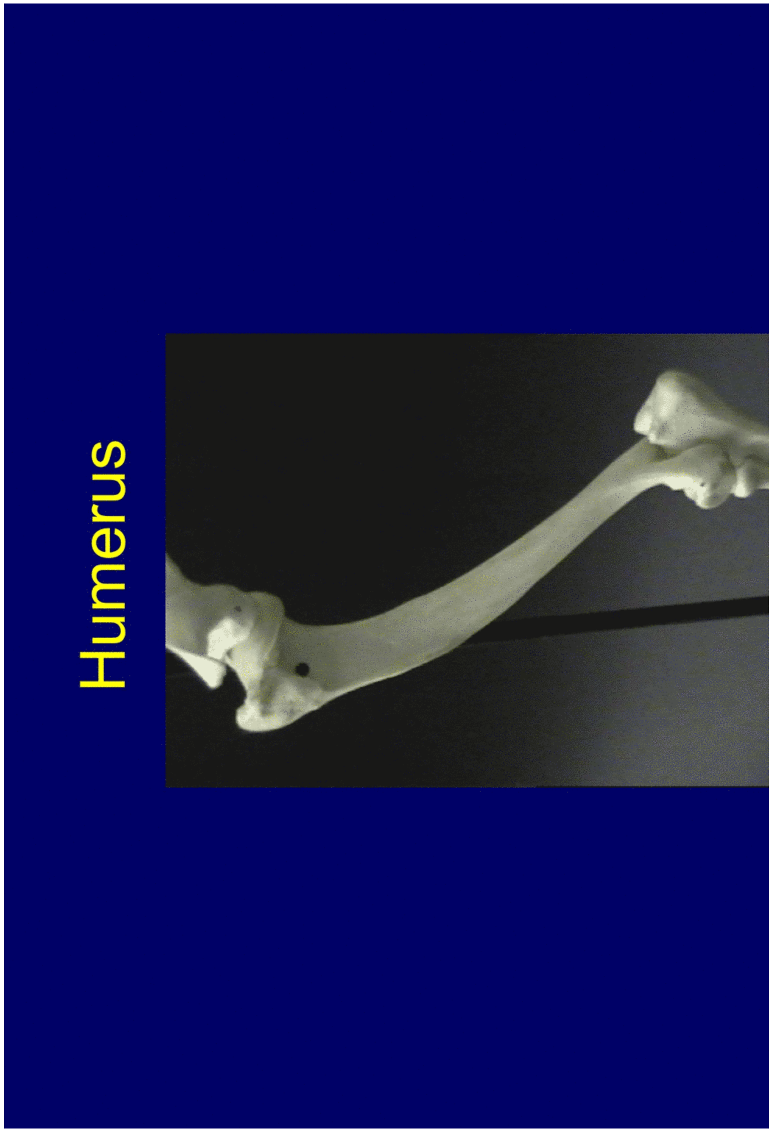

Male-Female Differences
Areal BMD
Growth
Ageing
Males
Females
Volumetric BMD
Males
Females
Volumetric BMD
2
20
M
F
Puberty
Seeman, E. (2001) *J Clin Endocrinol Metab* **86:** 4576

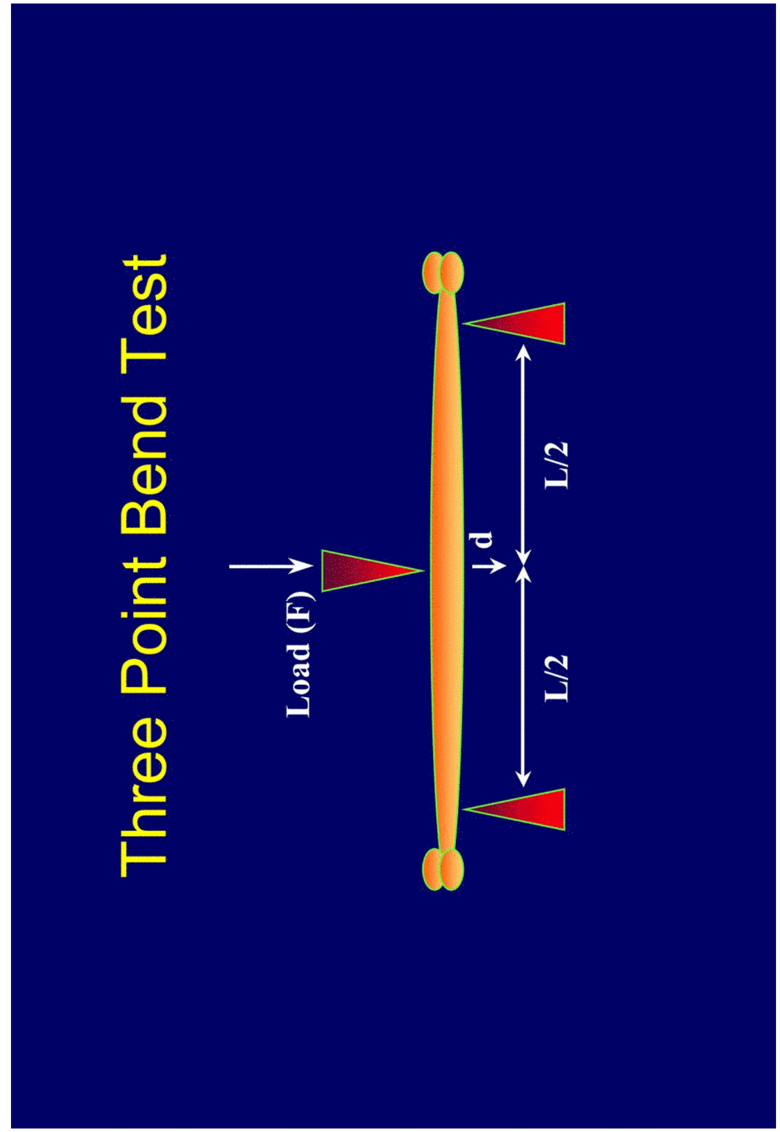
Mechanotransduction and Adult Skeletal Development

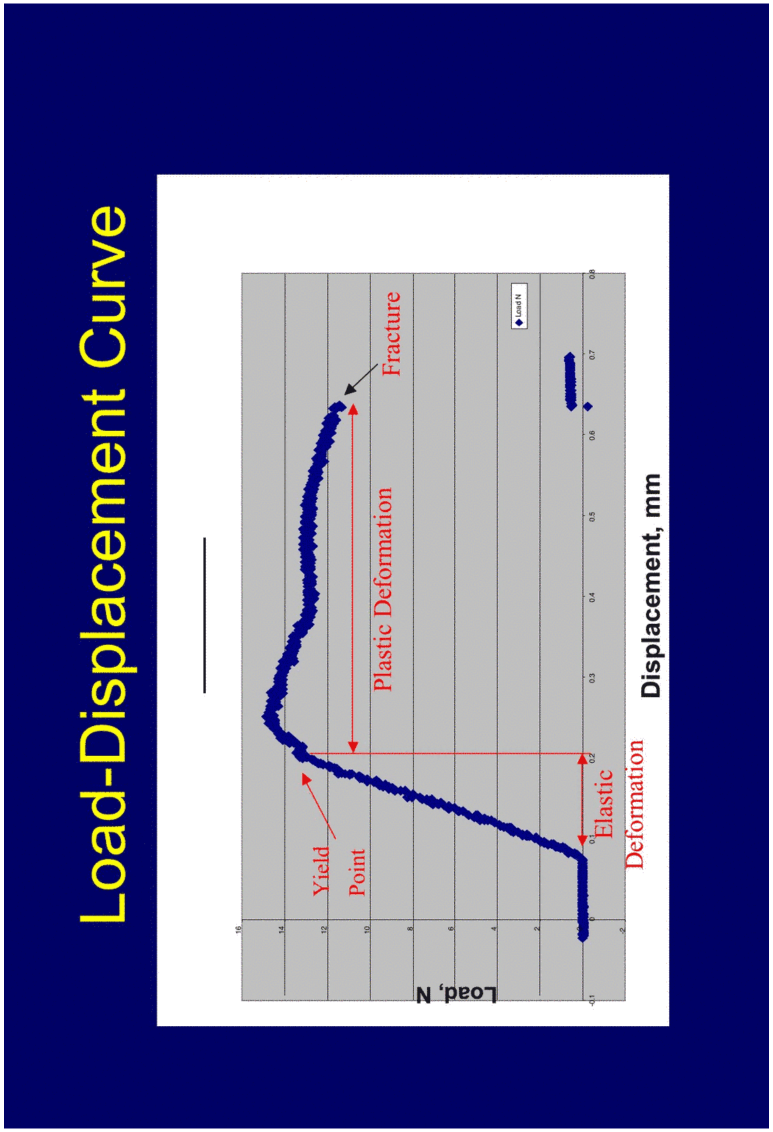
- Data from many labs show that many of the changes outlined in the last 2 slides are responses to mechanical loads applied to the bones.
- There are strain differences in mechanical responsiveness in mice.
- Mediators of mechanical load include the *Wnt-β catenin* pathway, NO, and Pg E

Longbow




Humerus


Three Point Bend Test
Load (F)
d
L/2
L/2

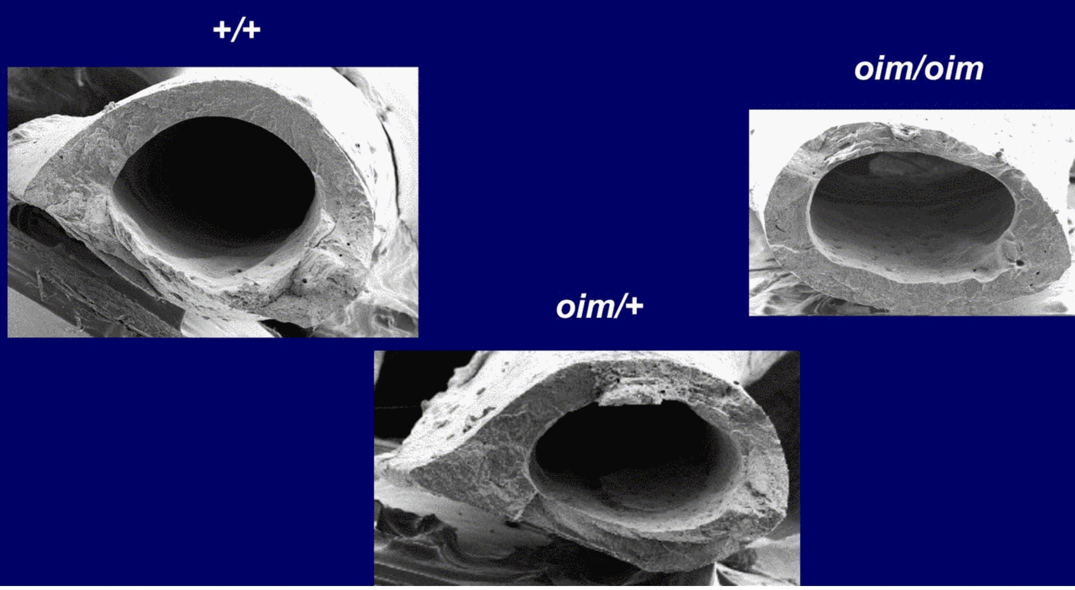

Load-Displacement Curve
Load, N
Displacement, mm
Yield Point
Elastic Deformation
Plastic Deformation
Fracture


Skeletal Deformity in Type III OI
From N. P. Camacho

Mouse OI

- There are several mouse models for OI, some naturally occurring and some engineered
- *Col1a2*^{oim} is a naturally occurring mutation in the gene encoding the α2 chain, and results in a chain deficiency form of disease
- Mice with 1 mutant allele have mild disease, while those with 2 mutant alleles have severe disease
- Bones show significantly reduced post-yield deflection

Fracture Surfaces in *Col1a2*^{oim}



Young's Modulus in *Col1a2^{oim}*

	17 weeks	11 weeks
+/+	30 ± 4	19 ± 4
oim/+	35 ± 2	18 ± 2
oim/ oim	ND	35 ± 2

GPa ± SEM

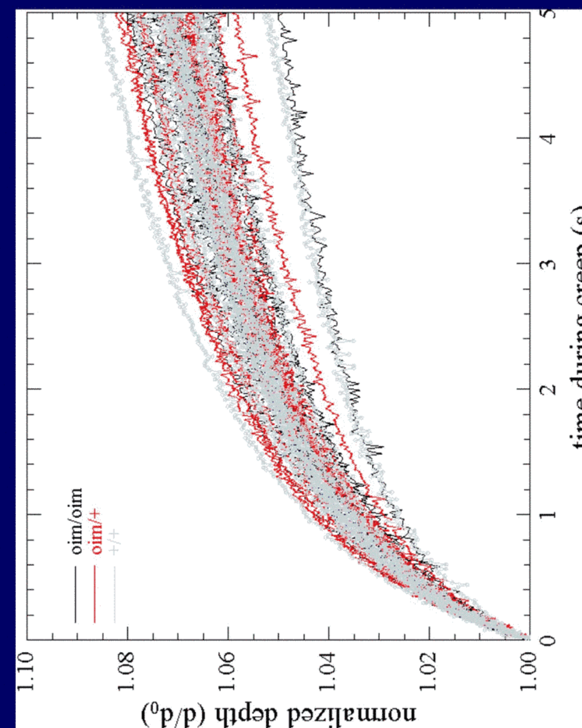
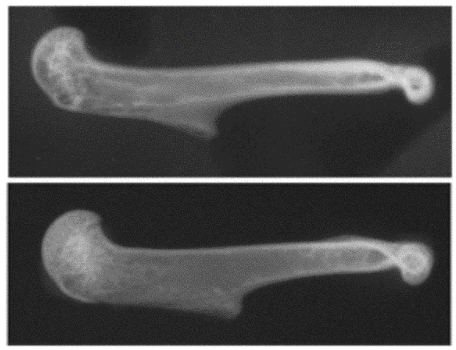


Figure 5. Representation of creep from time vs depth data for the three Col1a2 genotypes

Humeral Dimensions in C3H/DiSnA and C57BL/10ScSnA

A

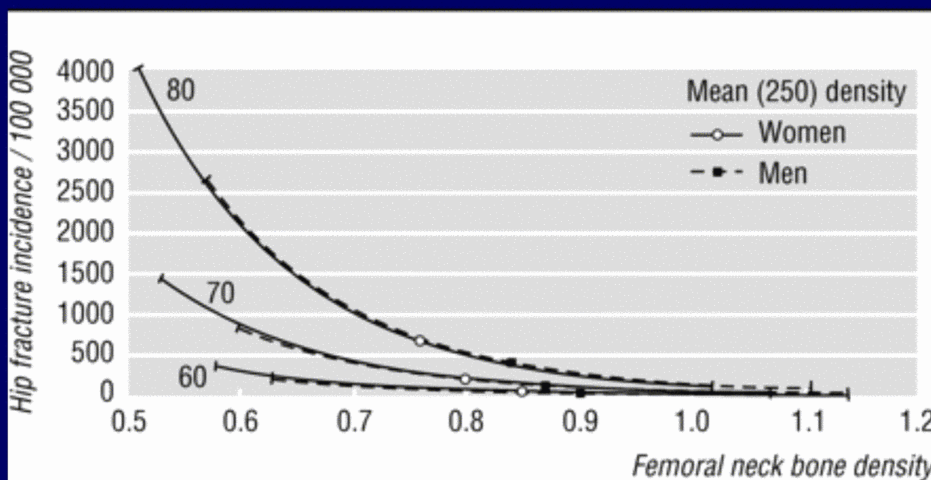
B



Different Optimization "Strategies"

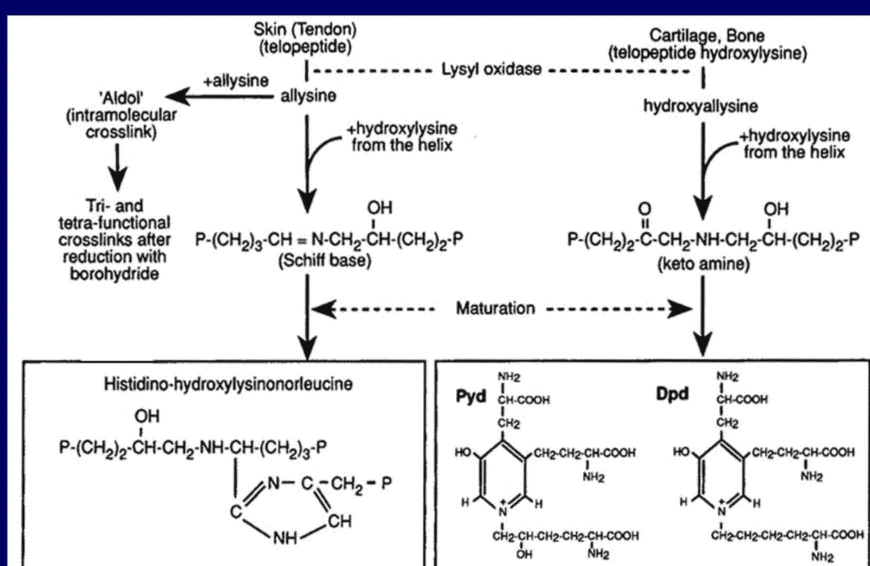
- Less bone tissue, bigger diameters
- More bone tissue, smaller diameters
- There are also inherent differences in tissue strength and stiffness, adding to complexity
- There is also a SUPERIMPOSED metabolic function of mineral homeostasis. This too drives bone remodeling. Relative contributions of mechanical and metabolic stimuli to bone remodeling are poorly understood.

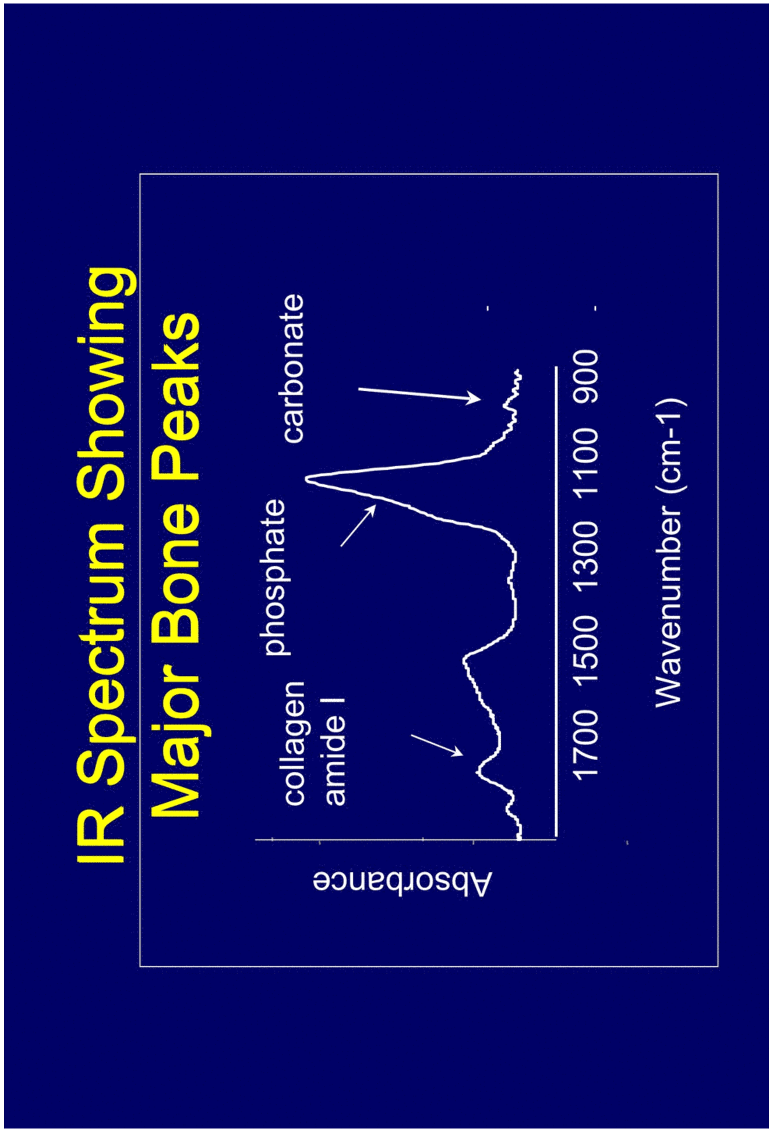
Age Increases Hip Fracture Risk

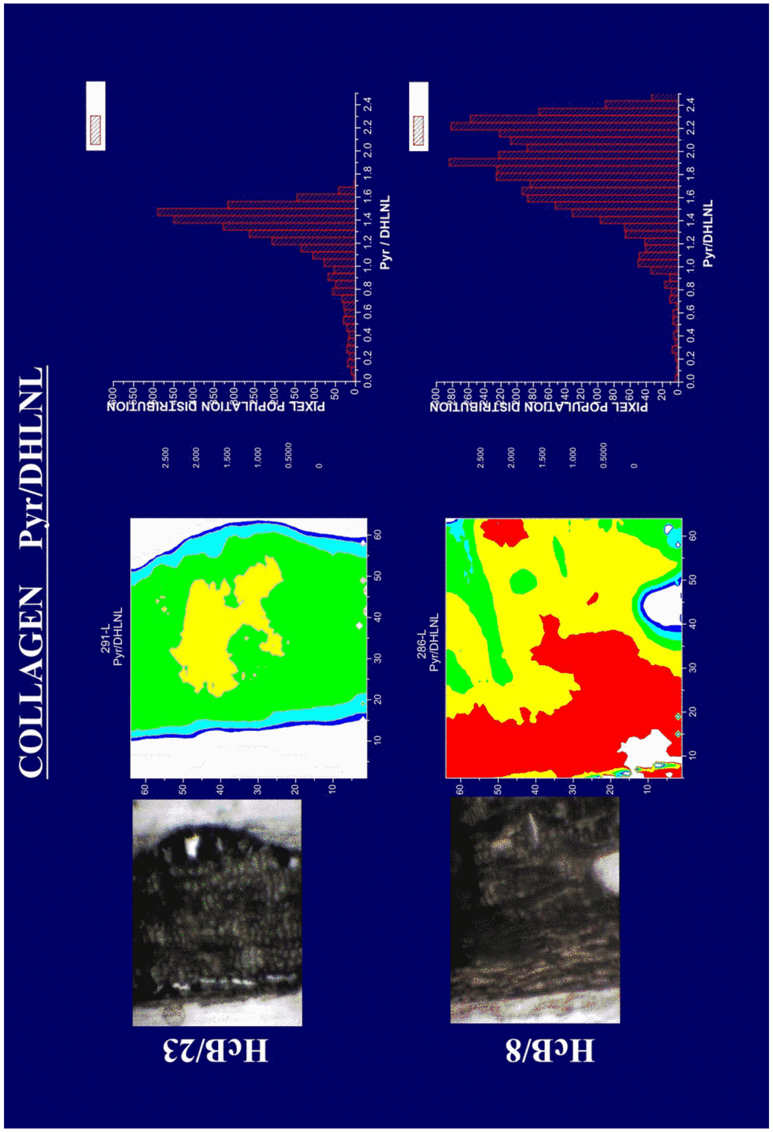


De Laet, C.E.D.H. *et al.*(1997) *BMJ* **315:** 221

FTIR Can Probe XL Chemistry



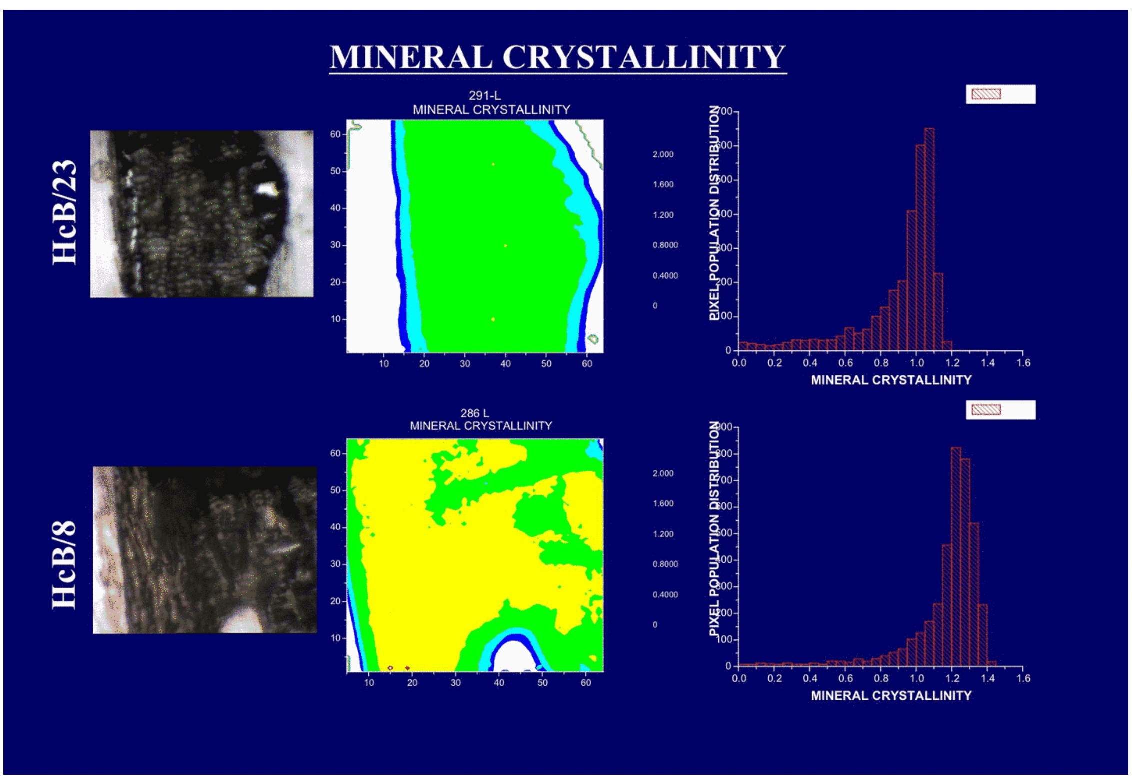

IR Spectrum Showing
Major Bone Peaks
collagen
amide I
phosphate
carbonate
Absorbance
1700 1500 1300 1100 900
Wavenumber (cm-1)


COLLAGEN Pyr/DHLNL
HcB/23
HcB/8
291-L
Pyr/DHLNL
286-L
Pyr/DHLNL
PIXEL POPULATION DISTRIBUTION
Pyr / DHLNL
PIXEL POPULATION DISTRIBUTION
Pyr/DHLNL

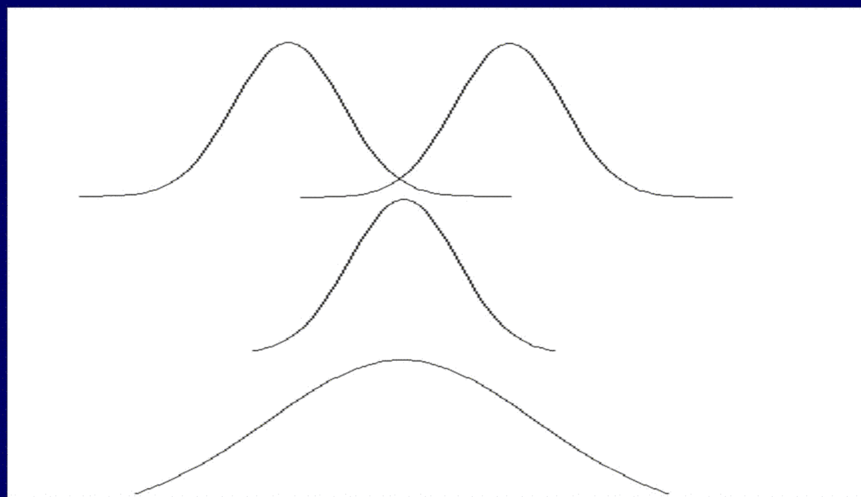
Nanoindentation HcB/23 & HcB/8

	HcB/23	HcB/8	P
Hardness	0.4 ± 0.1	0.7 ± 0.1	4×10^{-5}
Young's Modulus	21 ± 2	25 ± 2	0.046

GPa ± SEM



Intercross QTL Mapping



Acknowledgments

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  - Emily Chao
  - Tyriina O'Neil
  - Jon Vu
  - Don Stone
- HSS
  - Jason Wexler
  - Raj Gupta
  - Todd Baldini
  - Nancy Camacho

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