Principles of Bone Biology

THIRD EDITION

Volume 1

EDITED BY

John P. Bilezikian

Lawrence G. Raisz

T. John Martin

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Dedication

Gideon A. Rodan

We pay special tribute in this Third Edition of *Principles of Bone Biology* to one of the original three editors, Gideon Rodan, who passed away after a long illness on January 1, 2006. Gideon was a wonderful scientist who made outstanding contributions to our understanding of bone cell biology and to the treatment of metabolic bone diseases. His quiet but highly effective leadership style, superb intellect and major scientific achievements brought together bone and mineral investigators from all over the world. He was a beloved friend whose insight, empathy and sense of humor enriched our lives. Gideon's wisdom and breadth of knowledge were invaluable in selecting and evaluating the contributions to the first two editions of this book.

Gideon's education in mathematics and basic sciences in Israel, and his PhD at the Weitzman Institute on physicochemical aspects of mineral metabolism, provided the fuel for a career of sustained achievement and scholarship. He began his academic career at the University of Connecticut Dental School, rapidly became Chairman of the Department of Oral Biology, and built a program of research that brought that School to great prominence. He was a mentor supreme, with a large number of students, post-doctoral trainees and close colleagues who went on to have successful careers. They remained intensely loyal to him. A former President of the American Society of Bone and Mineral Research (ASBMR), Gideon was also the first recipient of the ASBMR Excellence in Mentorship award, an Award that has been named for him in perpetuity. After moving to the pharmaceutical industry in 1984 to lead research and development in bone biology and osteoporosis at Merck, Gideon fulfilled one of his obligations to that position many times over by selecting and then developing alendronate as a treatment for osteoporosis. This achievement set the bar for all future drug development programs in osteoporosis. Most remarkably at Merck, however, Gideon retained and developed even further the rigorous academic approach to bone biology that had always characterized him, wherever he was. In his never-ending quest to teach, to train, and to learn, Gideon was helped enormously by his wife, Sevgi, also his lifelong co-worker.

We all owe much to the innovative thought that Gideon brought to all levels of bone and mineral research. His great contributions directed our thinking and our concepts for an entire generation that has followed him. Gideon would have contributed as much to this third Edition as he did to the first two Editions. It is with the greatest admiration and respect that we dedicate this Third Edition of *Principles of Bone Biology* to his memory.

T. J. Martin, L. G. Raisz and J. P. Bilezikian.

Contributors

Tamara Alliston (2:1145) Department of Orthopedic Surgery, University of California, San Francisco, California 94143

Maria Almeida (1:237) Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

Andrew Arnold (2:1311) Center for Molecular Medicine and Division of Endocrinology and Metabolism, University of Connecticut School of Medicine, Farmington, Connecticut 06030

Jane E. Aubin (1:85) Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada

Roland Baron (1:221) Professor and Chair, Departments of Oral Medicine, Infection and Immunology, Harvard School of Dental Medicine and Professor; Department of Medicine, Harvard Medical School, Endocrine Unit, Massachusetts General Hospital, 188 Longwood Avenue, REB310, Boston, Massachusetts 02115

Teresita Bellido (1:237) Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

John P. Bilezikian (2:1801, 1:639, 1:657, 2:1635) Departments of Medicine and Pharmacology, College of Physicians and Surgeons, Columbia University, New York 10032

Alessandro Bisello (1:665) Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Katherine Blackwell (2:1235, 2:1635) New England Musculoskeletal Institute, University of Connecticut Health Center, Farmington, Connecticut, 06030

Glen M. Blake (2:1883) King's College London School of Medicine, London, United Kingdom

Lynda F. Bonewald (1:153, 2:1145) Department of Oral Biology, School of Dentistry, University of Missouri, Kansas City, Missouri 64108

Cesare Bordi (2:1345) Department of Pathology and Laboratory Medicine, Section of Anatomic Pathology, University of Parma, 1-43100 Parma, Italy

George Bou-Gharios (1:285) Imperial College London, Hammersmith Campus, London, United Kingdom

Roger Bouillon (2:983) Katholieke Universiteit Leuven, Laboratory for Experimental Medicine and Endocrinology, and Department of Obstetrics and Gynecology, Leuven, Belgium

Mary L. Bouxsein (1:29) Orthopedic Biomechanics Laboratory, Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts

Jeffrey D. Brady (1:319) TMRC Laboratory, University of Dundee, Dundee, Scotland

Maria Luisa Brandi (2:1345) Department of Internal Medicine and Regional Center for Hereditary Endocrine Tumors, Azienda Ospedaliera Universitaria Careggi, University of Florence, 6-50139 Florence, Italy

F. Richard Bringhurst (1:555) The Endocrine Unit and the Department of Medicine, The Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

Felix Bronner (1:515) The University of Connecticut Health Center, Farmington, Connecticut 06030-6125

Edward M. Brown (1:533, 2:1327) Endocrine-Hypertension Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Henry U. Bryant (1:887) Musculoskeletal Research, Lilly Research Laboratories, Eli Lilly and Company, d/c 0424, Indianapolis, Indiana 46285

Ernesto Canalis (2:1095) Saint Francis Hospital and Medical Center, University of Connecticut School of Medicine, Hartford, Connecticut

Shilpa Choudhary (2:1235, 2:1635) New England Musculoskeletal Institute, University of Connecticut Health Center, Farmington, Connecticut 06030

Sylvia Christakos (1:779) Department of Biochemistry and Molecular Biology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey

Roberto Civitelli (1:425) Washington University in St. Louis, Departments of Medicine and Cell Biology and Physiology, Division of Bone and Mineral Diseases, St. Louis, Missouri

Stephen Clark (2:1841) Department of Genetics and Developmental Biology University of Connecticut Health Center, Farmington, Connecticut

Thomas L. Clemens (1:733) Division of Molecular and Cellular Pathology, Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama

Michael T. Collins (2:1453) Craniofacial and Skeletal Diseases Branch, National Institute for Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland

Jill Cornish (1:837) Department of Medicine, University of Auckland, Auckland, New Zealand

Felicia Cosman (2:1769) Department of Medicine, Columbia University, New York

Serge Cremers (2:1857) Department of Medicine, Endocrinology, College of Physicians and Surgeons, Columbia University, New York

Sarah L. Dallas (2:1145) Department of Oral Biology, School of Dentistry, University of Missouri, Kansas City, Missouri 64108

Benoit de Crombrugghe (1:285) The University of Texas M. D. Anderson Cancer Center, Houston, Texas

David W. Dempster (1:447, 2:1661) Regional Bone Center, Helen Hayes Hospital, West Haverstraw, New York, and Department of Pathology, College of Physicians and Surgeons, Columbia University, New York

David T. Denhardt (1:351) Department of Cell Biology and Neuroscience, Rutgers University, Piscataway, New Jersey

Marc K. Drezner (1:465) Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism, University of Wisconsin, Madison, Wisconsin 53792

Patricia Ducy (2:1059) Department of Pathology, Columbia University, College of Physicians and Surgeons, New York

Le T. Duong (1:221) Department of Bone Biology and Osteoporosis, Merck Research Laboratories, West Point, Pennsylvania 19846

Frank H. Ebetino (2:1737) Procter and Gamble Pharmaceuticals, Mason, Ohio

Claire M. Edwards (2:1391) Vanderbilt Center for Bone Biology, Vanderbilt University, Nashville, Tennessee 37232-0575, USA

James R. Edwards (2:1391) Vanderbilt Center for Bone Biology, Vanderbilt University, Nashville, Tennessee 37232-0575, USA

Ghada El-Hajj Fuleihan (2:1327) Calcium Metabolism and Osteoporosis Program, American University of Beirut, Lebanon

Klaus Engelke (2:1905) Institute of Medical Physics, University of Erlangen, Germany Synarc Hamburg, Germany and San Francisco, California

Alberto Falchetti (2:1345) Department of Internal Medicine and Regional Center for Hereditary Endocrine Tumors, Azienda Ospedaliera Universitaria Careggi, University of Florence, 6-50139 Florence, Italy

Lorraine A. Fitzpatrick (1:657) Research and Development, Musculoskeletal Diseases, GlaxoSmithKline, King of Prussia, Pennsylvania

Ignac Fogelman (2:1883) King's College London School of Medicine, London, United Kingdom

Peter A. Friedman (1:665) Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Robert F. Gagel (1:813) Department of Endocrine Neoplasia and Hormonal Disorders, Division of Internal Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Laura W. Gamer (2:1167) Department of Developmental Biology, Harvard School of Dental Medicine, Boston, Massachusetts 02115

Thomas J. Gardella (1:555) The Endocrine Unit and the Department of Medicine, The Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

Patrick Garnero (2:1857) INSERM Research Unit 664 and Synarc Molecular Markers, Lyon, France

Harry K. Genant (2:1905) Synarc Hamburg, Germany and San Francisco, California; Department of Radiology, University of California, San Francisco, California

Luigi Gennari (2:1801) Department of Internal Medicine, Endocrine-Metabolic Sciences and Biochemistry, University of Siena, Siena, Italy

David Goltzman (2:1375) Calcium Research Laboratory and Department of Medicine, McGill University and Royal Victoria Hospital of the McGill University Health Centre, Montreal, Quebec, Canada H3A 141

William G. Goodman (2:1479) Nephrology Therapeutic Area, Amgen Inc., Thousand Oaks, California

Leland Graves III (2:955) Division of Endocrinology, Metabolism and Genetics, University of Kansas Medical Center, Kansas City, Kansas 66103

Naveen A. T. Hamdy (1:139) Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands

David A. Hanley (2:1661) Department of Medicine, Division of Endocrinology & Metabolism, Faculty of Medicine, University of Calgary, Alberta, Canada

Mohammad Q. Hassan (1:263) Department of Cell Biology and UMass Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts

Robert P. Heaney (2:1697) Creighton University, Omaha, Nebraska

Hunter Heath III (2:1327) Division of Endocrinology and Metabolism, Indiana University School of Medicine, Indianapolis, Indiana

Miep H. Helfrich (1:385) School of Medicine and Dentistry, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD

Geoffrey N. Hendy (2:1311) Calcium Research Laboratory, and Hormones and Cancer Research Unit, Royal Victoria Hospital, and Departments of Medicine, Physiology and Human Genetics, McGill University, Montreal, Quebec, Canada H3A 141

Anthony B. Hodsman (2:1661) Department of Medicine and the Lawson Health Research Institute, St. Joseph's Health Centre, and the University of Western Ontario, London, Ontario, Canada

W. Hofstetter (2:1197) Department Clinical Research, University of Bern, Murtenstrasse 35, 3010 Bern, Switzerland

Michael F. Holick (1:795) Boston University School of Medicine, Boston, Massachusetts

William C. Horne (1:221) Department of Oral Medicine, Infection and Immunology, Harvard School of Dental Medicine, Boston, Massachusetts 02115

Mark C. Horowitz (2:1209) Departments of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, Connecticut; and the Department of Medicine, The University of Connecticut Health Center, Farmington, Connecticut

Michael A. Horton (1:385) The London Centre for Nanotechnology, University College London, London, United Kingdom

Mimi I. Hu (1:813) Department of Endocrine Neoplasia and Hormonal Disorders, Division of Internal Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

Marja M. Hurley (2:1103) Department of Medicine, Division of Endocrinology and Metabolism, The University of Connecticut Health Center, Farmington, Connecticut 06032

Urszula T. Iwaniec (1:855) Department of Nutrition and Exercise Sciences Oregon State University, Corvallis, Oregon

Amjad Javed (1:263) Department of Cell Biology and UMass Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts

Suzanne M. Jan de Beur (2:1549) Department of Medicine, Division of Endocrinology and Metabolism, The Johns Hopkins University School of Medicine, 5200 Eastern Avenue, Mason F. Lord Building, Suite 4300, Baltimore, Maryland

Robert L. Jilka (1:237) Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

Mark L. Johnson (1:121) Department of Oral Biology, UMKC School of Medicine, 650 East 25th Street, Kansas City, Missouri 64108

Glenville Jones (2:1777) Department of Biochemistry, Queen's University, Kingston, Ontario, Canada

Niklas R. Jørgensen (1:425) Research Center for Ageing and Osteoporosis, Department of Rheumatology and Geriatrics, Copenhagen University Hospital Glostrup, Glostrup, Denmark

Stefan Judex (2:1819) Department of Biomedical Engineering, Psychology A, State University of New York at Stony Brook, Stony Brook, New York

Harald Jüppner (1:555, 2:1431) Endocrine Unit and Pediatric Nephrology Unit, Department of Medicine and MassGeneral Hospital for Children, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

Andrew C. Karaplis (1:53) Division of Endocrinology, Department of Medicine and Lady Davis Institute for Medical Research, Sir Mortimer B. Davis-Jewish H. General Hospital, McGill University, Montréal, Canada

Gerard Karsenty (1:109) Department of Genetics and Development, Columbia University Medical Center, New York 10027-6902

L. Lyndon Key Jr. (2:1561) Department of Pediatrics, General Clinical Research Center, Medical University of South Carolina, Charleston, South Carolina

Sundeep Khosla (2:1801) Department of Endocrinology, Metabolism, and Nutrition, Mayo Clinic and Foundation, Rochester, Minnesota 55905

J. Klein-Nulend (1:153) Department of Oral Cell Biology, ACTA-Vrije Universiteit, 1081 BT Amsterdam, The Netherlands

Barbara E. Kream (2:955) Department of Medicine, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, Connecticut 06030-1850

Yasuhiro Kobayashi (1:175) Division of Hard Tissue Research, Institute for Oral Science, Matsumoto Dental University, Shiojiri 399-0781, Japan

Stavroula Kousteni (1:639) Department of Medicine, College of Physicians and Surgeons, Columbia University, New York

Christopher S. Kovacs (1:713) Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland, Canada

Stephen M. Krane (1:367) Department of Medicine, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts

Henry M. Kronenberg (1:577) Endocrine Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114

Minnkyoung Lee (1:367) Department of Physiology and Biophysics, Robert Wood Johnson Medical School, Piscataway, New Jersey

Ulf H. Lerner (2:1025) Department of Oral Cell Biology, Umeå University, Umeå, Sweden

Jane B. Lian (1:263) Department of Cell Biology and UMass Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts

Uri A. Liberman (2:1533) Department of Physiology and Pharmacology and the Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel

Robert Lindsay (2:1769) Helen Hayes Hospital, West Haverstraw, New York

Joseph A. Lorenzo (2:1209) Departments of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, Connecticut; and the Department of Medicine, The University of Connecticut Health Center, Farmington, Connecticut

Clemens W. G. M. Löwik (1:139) Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands

Barbara P. Lukert (2:955) Division of Endocrinology, Metabolism and Genetics, University of Kansas Medical Center, Kansas City, Kansas 66103

Pernilla Lundberg (2:1025) Department of Oral Cell Biology, Umeå University, Umeå, Sweden

Conor C. Lynch (2:1391) Vanderbilt Center for Bone Biology, Vanderbilt University, Nashville, Tennessee 37232-0575

Karen M. Lyons (2:1167) Department of Orthopedic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California 90095

Carolyn M. Macica (1:733) Section of Endocrinology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

Jennifer Mammen (2:1549) Department of Medicine, Division of Endocrinology and Metabolism, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Stavros C. Manolagas (1:237) Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

Pierre J. Marie (2:1103) INSERM Unit 606 and University Paris 7, Lariboisiere Hospital, Paris, France

T. John Martin (1:175, 2:1635) St. Vincent Institute of Medical Research, Fitzroy, Victoria 3065, Australia

Stephen J. Marx (2:1345) Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

Paul D. Miller (2:1895) Distinguished Clinical Professor of Medicine, University of Colorado Health Sciences Center, Medical Director, Colorado Center for Bone Research, Lakewood, Colorado

Kohei Miyazono (2:1177) Department of Molecular Pathology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Martin Montecino (1:263) Departamento de Bioquimica Biologia Molecular, Facultad de Ciencias Biologicas, Universidad de Concepcion, Concepcion, Chile

Elise F. Morgan (1:29) Orthopaedic and Developmental Biomechanics Laboratory, Department of Aerospace and Mechanical Engineering, Boston University, Boston, Massachusetts

Gregory R. Mundy (2:1391) Vanderbilt Center for Bone Biology, Vanderbilt University, Nashville, Tennessee 37232-0575

Michael Naski (2:1103) Departments of Pathology and Biochemistry, University of Texas Health Science Center, San Antonio, Texas 78229

Dorit Naot (1:837) Department of Medicine, University of Auckland, Auckland, New Zealand

Tally Naveh-Many (1:577) Minerva Center for Calcium and Bone Metabolism, Nephrology Services, Hadassah Hebrew University Medical Center

Edward F. Nemeth (2:1711) 32 Elgin Avenue, Toronto, Ontario, Canada

Stephen A. Nesbitt (1:385) The London Centre for Nanotechnology, University College London, London, United Kingdom

Tianhua Niu (2:1069) Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Masaki Noda (1:351) Department of Molecular Pharmacology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

Anthony W. Norman (1:749) Department of Biochemistry and Division of Biomedical Sciences, University of California, Riverside, California

Charles A. O'Brien (1:237) Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

Roberto Pacifici (1:921) Division of Endocrinology, Metabolism, and Lipids Department of Medicine Emory University Atlanta, Georgia

Socrates E. Papapoulos (1:139) Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands

Nicola C. Partridge (1:367) Department of Physiology and Biophysics, Robert Wood Johnson Medical School, Piscataway, New Jersey

Emma Persson (2:1025) Department of Oral Cell Biology, Umeå University, Umeå, Sweden

Carol C. Pilbeam (2:1235, 2:1635) New England Musculoskeletal Institute, University of Connecticut Health Center, Farmington, Connecticut 06030

Lilian I. Plotkin (1:237) Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

John T. Potts, Jr. (1:555) The Endocrine Unit and the Department of Medicine, The Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

Sven Prevrhal (2:1905) Musculoskeletal Quantitative Imaging Research Group, University of California, San Francisco, California

Lawrence G. Raisz (2:1235, 2:1635) New England Musculoskeletal Institute, University of Connecticut Health Center, Farmington, Connecticut 06030

Stuart H. Ralston (2:1611) Rheumatic Diseases Unit, Molecular Medicine Centre, Western General Hospital, Edinburgh, United Kingdom

Ian R. Reid Department of Medicine, University of Auckland, Auckland, New Zealand

Alfred A. Reszka (2:1737) Department of Bone Biology and Osteoporosis Research, Merck Research Laboratories, Merck and Company Inc., West Point, Pennsylvania

David J. Rickard (1:855) Musculoskeletal Diseases Biology GlaxoSmithKline Research and Development, Collegeville, Pennsylvania

Ryan C. Riddle (1:733) Division of Molecular and Cellular Pathology, Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama

William L. Ries (2:1561) Department of Pediatrics, General Clinical Research Center, Medical University of South Carolina, Charleston, South Carolina

Pamela Gehron Robey (1:335) Craniofacial and Skeletal Diseases Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

Simon P. Robins (1:319) Matrix Biochemistry, Rowett Research Institute, Aberdeen, United Kingdom

Anke J. Roelofs (2:1737) Bone & Musculoskeletal Research Programme, University of Aberdeen, Aberdeen, United Kingdom

Michael J. Rogers (2:1737) Bone & Musculoskeletal Research Programme, University of Aberdeen, Aberdeen, United Kingdom

G. David Roodman (2:1599) Department of Medicine, Division of Hematology, University of Pittsburgh, and VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania

Clifford J. Rosen (2:1069) Maine Center for Osteoporosis Research and Education, St. Joseph Hospital, Bangor, Maine

Vicki Rosen (2:1167) Department of Developmental Biology, Harvard School of Dental Medicine, Boston, Massachusetts 02115

Michael Rosenblatt (1:595) Department of Physiology, Tufts University School of Medicine, Boston, Massachusetts

David W. Rowe (2:1511, 2:1841) Department of Genetics and Developmental Biology, University of Connecticut Health Center, Farmington, Connecticut

Clinton T. Rubin (2:1819) Department of Biomedical Engineering, Psychology A, State University of New York at Stony Brook, Stony Brook, New York

Janet Rubin (2:1819) Endocrine Division, Department of Medicine, University of North Carolina, Chapel Hill, North Carolina

Robert K. Rude (1:487) Keck School of Medicine University of Southern California, Los Angeles, California

R. Graham G. Russell (2:1737) The Oxford University Institute of Musculoskeletal Sciences, The Botnar Research Centre, Nuffield Department of Orthopaedic Surgery, Nuffield Orthopaedic Centre, Headington, Oxford, United Kingdom

Archana Sanjay (1:221) Department of Anatomy and Physiology, Temple University School of Medicine, Philadelphia, Pennsylvania 19140

Thorsten Schinke (1:109) Center for Biomechanics and Skeletal Biology, Department of Trauma, Hand, and Reconstructive Surgery, University Medical Center Hamburg Eppendorf, Hamburg, Germany

Ernestina Schipani (2:1431) Endocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114

Ego Seeman (1:3) Department of Endocrinology and Medicine, Austin Health University of Melbourne, Melbourne, Australia

Markus J. Seibel (2:1857) Bone Research Program, Anzac Research Institute The University of Sydney, Sydney, Australia

Tomomasa Shimanuki (2:1177) Department of Molecular Pathology, Graduate School of Medicine, University of Tokyo, Tokyo 113–0033, Japan, and Drug Discovery Unit, R&D Laboratories, POLAPHARMA INC., Kanagawa 244-0812, Japan

Emi Shimizu (1:367) Department of Physiology and Biophysics, Robert Wood Johnson Medical School, Piscataway, New Jersey

Caroline Silve (2:1431) INSERM U. 773 and Laboratoire de Biochimie Hormonale et Génétique, Hopital and Faculté de Médecine Xavier Bichat, 75018 Paris, France

Justin Silver (1:577) Minerva Center for Calcium and Bone Metabolism, Nephrology Services, Hadassah Hebrew University Medical Center

Shonni J. Silverberg (1:657) Departments of Medicine, College of Physicians and Surgeons, Columbia University, New York

Stuart L. Silverman (2:1649) Cedars-Sinai/UCLA, Los Angeles, California

Frederick R. Singer (2:1599) John Wayne Cancer Institute, Saint John's Health Center, Santa Monica, California

Chan Soo Shin (1:425) Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

Thomas C. Spelsberg (1:855) Department of Biochemistry and Molecular Biology, Mayo Clinic and Foundation, Rochester, Minnesota

Joseph P. Stains (1:425) Department of Orthopedics, University of Maryland School of Medicine, Baltimore, Maryland

Gary S. Stein (1:263) Department of Cell Biology and UMass Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts

Janet L. Stein (1:263) Department of Cell Biology and UMass Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts

Gudrun Stenbeck (1:385) Centre for Cell and Chromosome Biology, Heinz Wolff Building, Brunel University, Uxbridge, United Kingdom

Julie A. Sterling (2:1391) Vanderbilt Center for Bone Biology, Vanderbilt University, Nashville, Tennessee 37232-0575

Paula H. Stern (1:935) Department of Molecular Pharmacology and Biological Chemistry, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Andrew F. Stewart (1:713) University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Tatsuo Suda (1:175) Research Center for Genomic Medicine, Saitama Medical University, Saitama 350-1241, Japan

Naoyuki Takahashi (1:175) Division of Hard Tissue Research, Institute for Oral Science, Matsumoto Dental University, Shiojiri, Japan

Masamichi Takami (1:175) Department of Biochemistry, School of Dentistry, Showa University, Tokyo 142-8555, Japan

Hiroshi Takayanagi (1:211) Department of Cell Signaling, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

Shu Takeda (2:1059) Department of Orthopaedic Surgery, Graduate School, 21st Century Center of Excellence Program, Tokyo Medical and Dental University, Tokyo, Japan

R.V. Thakker (2:1415) OCDEM, Nuffield Department of Clinical Medicine, University of Oxford, Headington, Oxford, United Kingdom

Francesco Tonelli (2:1345) Surgery Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy

Dwight A. Towler (2:1133) Department of Medicine, Center for Cardiovascular Research, Division of Bone and Mineral Diseases, Washington University in St. Louis, Missouri 63110

Russell T. Turner (1:855) Department of Nutrition and Exercise Sciences Oregon State University, Corvallis, Oregon

Nobuyuki Udagawa (1:175) Division of Hard Tissue Research, Institute for Oral Science, Matsumoto Dental University, Shiojiri, Japan

H. Kalervo Väänänen (1:193) Department of Anatomy, Institute of Biomedicine, University of Turku, Turku, Finland

Rutger L. van Bezooijen (1:139) Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands

André J. van Wijnen (1:263) Department of Cell Biology and UMass Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts

Johan Verhaeghe (2:983) Katholieke Universiteit Leuven, Laboratory for Experimental Medicine and Endocrinology, and Department of Obstetrics and Gynecology, Leuven, Belgium

Patricia H. Watson (2:1661) Department of Medicine and the Lawson Health Research Institute, St. Joseph's Health Centre, and the University of Western Ontario, London, Ontario, Canada

Lee S. Weinstein (2:1453) Metabolic Diseases Branch, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Robert S. Weinstein (1:237) Division of Endocrinology and Metabolism, Center for Osteoporosis and Metabolic Bone Diseases, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, Arkansas 72205

Michael P. Whyte (2:1573) Center for Metabolic Bone Disease and Molecular Research, Shriners Hospitals for Children, St. Louis, Missouri, and Division of Bone and Mineral Diseases, Washington University School of Medicine at Barnes-Jewish Hospital, St. Louis, Missouri

Sunil J. Wimalawansa (2:1275) Division of Endocrinology/Regional Osteoporosis Center, Department of Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, New Jersey 08903

Kristine M. Wiren (2:1001) Oregon Health and Science University, Portland VA Medical Center, Portland, Oregon

Angela Wittelsberger (1:595) Department of Physiology, Tufts University School of Medicine, Boston, Massachusetts

John J. Wysolmerski (1:713) Yale University School of Medicine, New Haven, Connecticut

Daniel W. Young (1:263) Novartis Institutes for BioMedical Research, Cambridge, Massachusetts

Sayyed K. Zaidi (1:263) Department of Cell Biology and UMass Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts

Haibo Zhao (1:193) Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri

Junling Zhuang (2:1391) Vanderbilt Center for Bone Biology, Vanderbilt University, Nashville, Tennessee 37232-0575

Preface to the Third Edition

The two previous editions of *Principles of Bone Biology* have been well received. They have not only provided a resource for investigators already working in the field, but have helped new investigators rapidly "get up to speed" in developing their projects and grant proposals. The rapid progress in our field in the last 6 years mandates that we update this text, so that it can continue to serve as a basic resource.

In this third edition, most of the chapters have been prepared by authors of the previous edition but the chapters have been extensively revised and updated. In addition a number of new authors have gracefully consented to join us. This has involved consolidation, reconfiguration, and reorganizing the information being presented. The two-volume format has been retained along with approximately the same text length. The loss of Gideon Rodan has been deeply felt by all of us and these volumes are dedicated to him. In the spirit that Gideon would have applauded, we are delighted that his close colleague and friend Jack Martin has joined us as Editors to continue this work to which Gideon contributed so much. Finally we would like to acknowledge the help of the staff at Elsevier-Academic Press who have worked valiantly to maintain schedules and have enabled us to complete this third edition. We trust that the book will be successful in providing a complete repository of the most current and accurate information in the field of bone biology.

John P. Bilezikian
Lawrence G. Raisz
T. John Martin

Preface to the First Edition

The world of modern science is undergoing a number of spectacular events that are redefining our understanding of ourselves. As with any revolution, we should take stock of where we have been, where we are, and where we are going. Our special world of bone biology is participating in and taking advantage of the larger global revolution in modern science. Often with shocking but delightful suddenness, we are gaining new insights into difficult issues, discovering new concepts to explain old observations, developing new approaches to perennial mysteries, and applying novel technological advances from other fields to our own. The pace with which the bone world is advancing is impressive not only to the most ardent optimists, who did not expect so much so soon, but also to the more sober minded who, only several years ago, would have brushed off the notion that progress could come with such lightening speed.

The rationale for this book is rooted in the recognition of the revolution in bone biology. We need a new repository of knowledge, bringing us both to the core and to the edge of our universe. Our goal is to provide complete, truly up-to-date, and detailed coverage of this exciting and rapidly developing field. To achieve this, we assembled experts from all over the world and asked them to focus on the current state of knowledge and the prospects for new knowledge in their area of expertise. To this end, *Principles of Bone Biology* was conceived. It is designed to be useful to students who are becoming interested in the field and to young investigators at the graduate or postgraduate level who are beginning their research careers. It is also designed for more established scientists who want to keep up with the changing nature of our field, who want to mine this lode to enrich their own research programs, or who are changing their career direction. Finally, this book is written for anyone who simply strives for greater understanding of bone biology.

This book is intended to be comprehensive but readable. Each chapter is relatively brief. The charge to each author has been to limit size while giving the reader information so complete that it can be appreciated on its own, without necessary recourse to the entire volume. Nevertheless, the book is also designed with a logic that might compel someone to read on, and on, and on!

The framework of organization is fourfold. The first 53 chapters, in a section titled "Basic Principles," cover the cells themselves: the osteoblast, the osteoclast, and the osteocyte; how they are generated; how they act and interact; what turns them on; what turns them off; and how they die. In this section, also, the biochemistry of collagenous and noncollagenous bone proteins is covered. Newer understandings of calcium, phosphorus, and magnesium metabolism and the hormones that help to control them, namely, parathyroid hormone, vitamin D metabolites, calcitonin, and related molecules, are presented. A discussion of other systemic and local regulators of bone metabolism completes this section.

The second section of this book, "Molecular Mechanisms of Metabolic Bone Diseases," is specifically devoted to basic mechanisms of a variety of important bone diseases. The intention of these 17 chapters is not to describe the diseases in clinical, diagnostic, or therapeutic terms but rather to illustrate our current understanding of underlying mechanisms. The application of the new knowledge summarized in Part I to pathophysiological, pathogenetic, and molecular mechanisms of disease has relevance to the major metabolic bone disorders such as osteoporosis, primary hyperparathyroidism, and hypercalcemia of malignancy as well as to the more uncommon disorders such as familial benign hypocalciuric hypercalcemia, pseudohypoparathyroidism, and osteopetrosis.

The third section of this book, "Pharmacological Mechanisms of Therapeutics," addresses the great advances that have been made in elucidating how old and new drugs act to improve abnormalities in bone metabolism. Some of these drugs are indeed endogenous hormones that under specified circumstances are useful therapies: estrogens, vitamin D, calcitonin, and parathyroid hormone are representative examples. Others agents such as the bisphosphonates, fluoride, and calcium are reviewed. Finally, agents with therapeutic potential but still in development such as calcimimetics, insulin-like growth factors, transforming growth factor, bone morphogenetic protein, and fibroblast growth factor are presented with a view to the future. The intent of this 12-chapter section is not to provide step-by-step "how-to" instructions for the clinical uses of these agents. Such prescribing information for established

therapies is readily found in other texts. Rather, the underlying mechanisms by which these agents are currently believed to work is the central point of this section.

The fourth and final section of this book, "Methods in Bone Research," recognizes the revolution in investigative methodologies in our field. Those who want to know about the latest methods to clone genes, to knock genes out, to target genes, and to modify gene function by transfection and by transcriptional control will find relevant information in this section In addition, the selection and characteristics of growth conditions for osteoblastic, osteoclastic, and stem cells; animal models of bone diseases; assay methodologies for bone formation and bone resorption and surrogate bone markers; and signal transduction pathways are all covered. Finally, the basic principles of bone densitometry and bone biopsies have both investigative and clinical relevance. This 15-chapter section is intended to be a useful reference for those who need access to basic information about these new research technologies.

The task of assembling a large number of international experts who would agree to work together to complete this ambitious project was formidable. Even more daunting was the notion that we would successfully coax, cajole, and otherwise persuade authors of 97 chapters to complete their tasks within a six-month period. For a book to be timely and still fresh, such a short time leash was necessary. We are indebted to all the authors for delivering their chapters on time.

Finally, such a monumental undertaking succeeds only with the aid of others who helped conceive the idea and to implement it. In particular, we are grateful to Jasna Markovac of Academic Press, who worked tirelessly with us to bring this exciting volume to you. We also want to thank Tari Paschall of Academic Press, who, with Jasna, helped to keep us on time and on the right course. We trust our work will be useful to you whoever you are and for whatever reason you have become attracted to this book and our field. Enjoy the book. We enjoyed editing it for you.

John P. Bilezikian
Lawrence G. Raisz
Gideon A. Rodan

Part I

Basic Principles

Chapter 1

Modeling and Remodeling

The Cellular Machinery Responsible for the Gain and Loss of Bone's Material and Structural Strength

Ego Seeman

Department of Endocrinology and Medicine, Austin Health, University of Melbourne, Melbourne, Australia

INTRODUCTION

Propulsion against gravity requires levers. Bones are levers and must be stiff, that is, they must resist deformation. Impact loading imparts energy to bone. Because energy cannot be destroyed, it must be stored or dissipated. Thus, bone must also be flexible in order to absorb energy by changing shape; it must be able to shorten and widen in compression and lengthen and narrow in tension without cracking (Currey, 2002). Bone must also be light to allow mobility.

The elastic properties of bone allow it to absorb energy by deforming reversibly when loaded (Lanyon *et al.,* 1976; Turner *et al.,* 2006). If the load imposed exceeds bones' ability to deform elastically, plastic deformation occurs but this is irreversible; it is accompanied by a permanent change shape with accumulation of microcracks that allow energy release (Currey, 2002). The ability to develop microdamage is a defense against the alternative, namely, a complete fracture, but microcracks compromise strength as they accumulate (Burr *et al.,* 1998). If both the elastic and plastic zones of deformation are exceeded, structural failure – fracture – occurs.

Bone achieves the paradoxical properties of stiffness yet flexibility, strength yet lightness through its material composition and its structural design – the way this material is fashioned in three-dimensional space containing "nothing" – void space. Excavation of a marrow cavity during growth confers strength in tubular bones like the femur or tibia, which function mainly as levers, by shifting the mineralized cortical bone radially increasing resistance to bending (Ruff and Hayes, 1988). It also confers lightness by minimizing the mass needed to achieve this resistance to bending.

For structures like the vertebral body that must have greater flexibility than long bones, nature again takes advantage of void to achieve a different type of strength – the ability to deform (tolerate strain or change in length) without cracking. Lightness is achieved by fashioning the mineralized bone material with many voids; as a porous sponge-like structure of trabecular plates and sheets. Stiffness and the ability to tolerate large loads is sacrificed in favor of greater ability to deform – peak loads achievable are less than in tubular bones but the ability to absorb energy by changing length without cracking is greater.

Material Strength

Type 1 collagen is tough: It is distensible in tension but lacks resistance to bending so it needs to be stiffened. This is achieved by creating a composite of collagen plus mineral but more mineral is not necessarily better. Greater the mineral content produces greater the material stiffness, but the ability to deform and so absorb and store energy decreases as a result. For a given increase in the percentage mineral ash, stiffness increase fivefold but work to fracture decreases fourteen-fold (Currey, 2002) (Fig. 1, upper panel).

Nature selects the mineral concentration most suited to the particular function a given bone *usually* performs. Ossicles in the ear are over 80% mineral, a feature selected for so that they can vibrate like tuning forks without storing energy in deformation (Fig. 1, lower panel). These bones sacrifice the ability to deform in favor of stiffness to transmit sound with high fidelity. The slightest deformation and they crack but deformation is unlikely because they are protected safely in the skull. On the other hand, deer antlers are less densely mineralized to facilitate deformation so energy can be absorbed like springs during head butting in mating season. Greater energy-absorbing ability of antlers is favored over stiffness but they do not need stiffness; they are not load-bearing (Currey, 1969).

The organization of the composite of mineral and collagen is incompletely understood. Although the mineral is the material that stiffens bone, it is also the most brittle component and must be protected. Collagen fibers contain

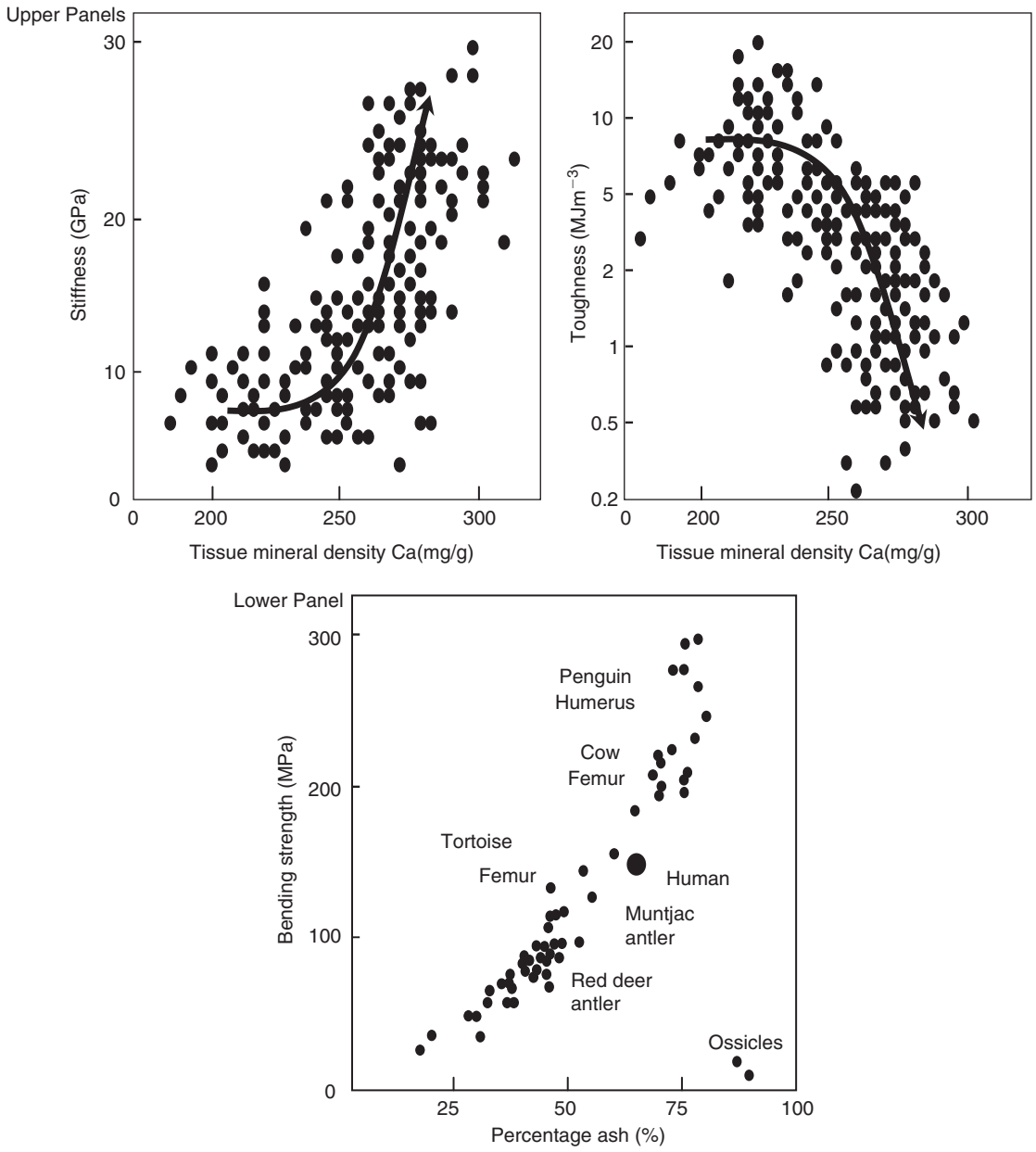

FIGURE 1 Upper panels: As tissue mineral content increases stiffness increases but toughness decreases. Adapted from Currey (2002). Lower panel: Ossicles of the ear are 90% mineral. They function as sound transducers and have little resistance to bending; they are brittle and will crack when slightly deformed. Antlers are about 40% mineral allowing them to deform without cracking. Adapted from Currey (1969).

mineral, interfibrillary matrix, and mineralized fibrils. The mineralized fibrils are composed of platelets of mineral and an intrafibrillary matrix phase of noncollagenous proteins. The brittle mineral confers stiffness and is protected during loading by energy absorption by collagen deformation and by noncollagenous proteins that dissipate energy by reversibly breaking intrahelical bonds that are "sacrificed" to provide "hidden" length (Fantner *et al.,* 2005; Gupta *et al.,* 2006) (Fig. 2). Stresses at the tissue, fiber, and mineral levels decrease in proportions of 12:5:2.

Structural Strength

During growth, the bone with its appropriate material composition is fashioned into three-dimensional masterpieces of biomechanical engineering. Although there is variability in the material composition of bone, this composition is similar in land-dwelling mammals (Keaveney *et al.,* 1998), so that most of the diversity in bone strength is the result of structural diversity that is obvious at the macroscopic level from bone to bone but the diversity in cross-sectional size,

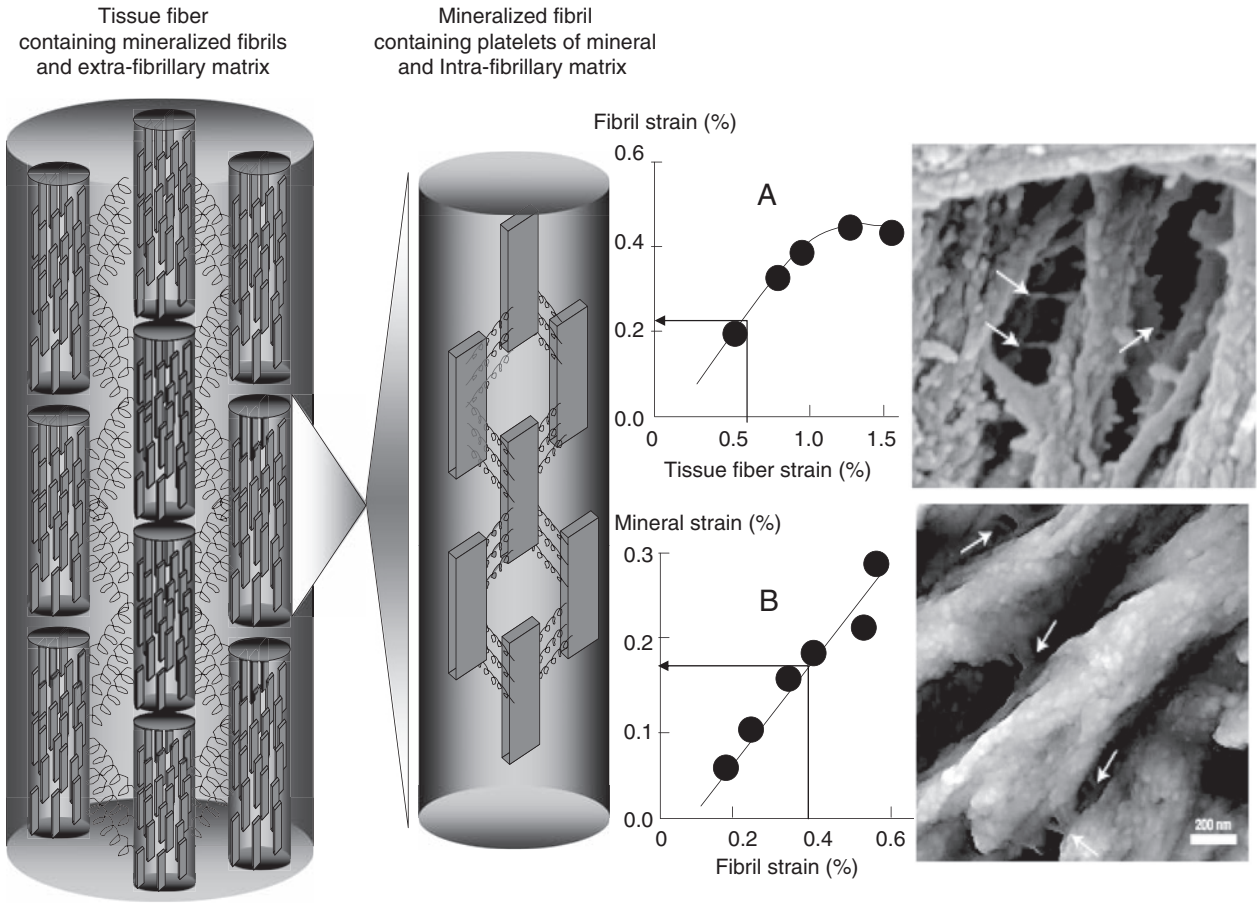

FIGURE 2 A collagen tissue fiber contains mineralized fibrils. The fibrils contain mineral platelets bound by noncollagenous proteins, helical structures that can absorb and dissipate energy during tensile strain by the breakage of sacrificial intra-helical bonds allowing uncoiling to provide "hidden length." This avoids overloading the mineral platelets. Graph A: Tissue fiber strain distributed to fibrils. Graph B: Fibrils absorb strain minimizing mineral strain. Adapted from Gupta *et al.* (2006). Images of noncollagenous glue like proteins. From Fantner *et al.* (2005).

shape, and the way its architecture is distributed in three-dimensional space from cross-section to cross-section as cortical and trabecular bone along a bone has only recently been given attention (Zebaze *et al.,* 2005; Zebaze *et al.,* 2007).

Structural diversity is largely due to individual differences in genetic makeup rather than individual differences in life style (Pocock *et al.,* 1987; Christian *et al.,* 1989). Fetal limb buds removed *in utero* and grown *in vitro* develop the shape of the proximal femur implying that bone shape is "imprinted" in the genetic material (Murray and Huxley, 1925). Studies in families and twins support this view (Seeman *et al.,* 1989; Seeman *et al.,* 1996). Although the many genes responsible for the diversity in bone's structural strength, and the contribution of environmental factors to this diversity, are largely undefined, the final pathway mediating genetic and environmental influences on structural diversity is the cellular machinery of bone modeling and remodeling (Parfitt, 1989).

BONE MODELING AND REMODELING DURING GROWTH AND THE ATTAINMENT OF PEAK STRENGTH

Bone *modeling* (construction) is the process by which bone is formed by osteoblasts without prior bone resorption. This process is vigorous during growth and produces changes in bone size and shape. Bone *remodeling* (reconstruction) occurs throughout life. Bone is first resorbed by osteoclasts and then formed in the same location by osteoblasts. These cells form the basic metabolic unit (BMU) that reconstructs bone in distinct locations on the three (endocortical, intracortical, and trabecular) components of its inner (endosteal) envelope and to a much lesser extent on the outer (periosteal) envelope (Orwoll *et al.,* 2003; Blizoites *et al.,* 2006).

Bone modeling and remodeling achieve strength for loading and lightness for mobility in two ways: by strategically depositing bone in locations where it is needed

to modify bone size and shape, and by removing bone from where it is not needed to avoid bulk. The enormous capacity of this cellular machinery to modify structure during growth is seen in the morphological differences between the playing and nonplaying arm of tennis players. Modeling and remodeling modifies bone size, shape, and mass distribution of the humerus of the playing arm without changing its mass (Haapasalo *et al.,* 2000; Bass *et al.*, 2002; Seeman, 2002). However, this ability to adapt structure to its loading circumstances after the completion of longitudinal growth is limited because periosteal apposition decreases precipitously and the age-related changes in remodeling occur that produce structural decay (see Section III).

The Purpose of Modeling and Remodeling During Growth – Optimizing Strength and Minimizing Mass

If bone had only to be strong it could achieve this with bulk – more mass, but mass takes time to grow, is costly to maintain and limits mobility. Bone also must serve a second need – lightness to facilitate mobility. Longer tubular bones need more mass to construct their length than shorter bones do, but wider and narrower cross-sections do not necessarily differ in the absolute amount of material needed to construct them (Zebaze *et al.,* 2007).

Although it seems obvious that the total cross-sectional area (cortical area plus marrow area) of a wider femoral neck or femoral shaft must be assembled with more mass, this is not the case. The total cross-sectional area of a tubular bone and its bone mass are independent; wider and narrower bone cross-sections are assembled using a similar amount of material (Fig. 3). Thus, larger cross-sections are assembled with less material relative to their size producing a lower apparent volumetric bone mineral density (vBMD) and so avoiding bulk. Smaller cross-sections are assembled with more material relative to their size, producing a higher vBMD while avoiding the fragility of slenderness.

Bulk is avoided in larger cross-sections by greater endocortical resorption, which excavates a correspondingly larger marrow cavity so that the endocortical envelope approximates the periosteal envelope; wider tubular bones are assembled with a relatively thinner cortex (producing the same cortical bone area because the thinner "ribbon" of cortex is distributed around a larger perimeter). By analogy, constancy of mass achieves a wider or narrower cylinder by rolling a sheet of paper with fewer or more rolls of the sheet.

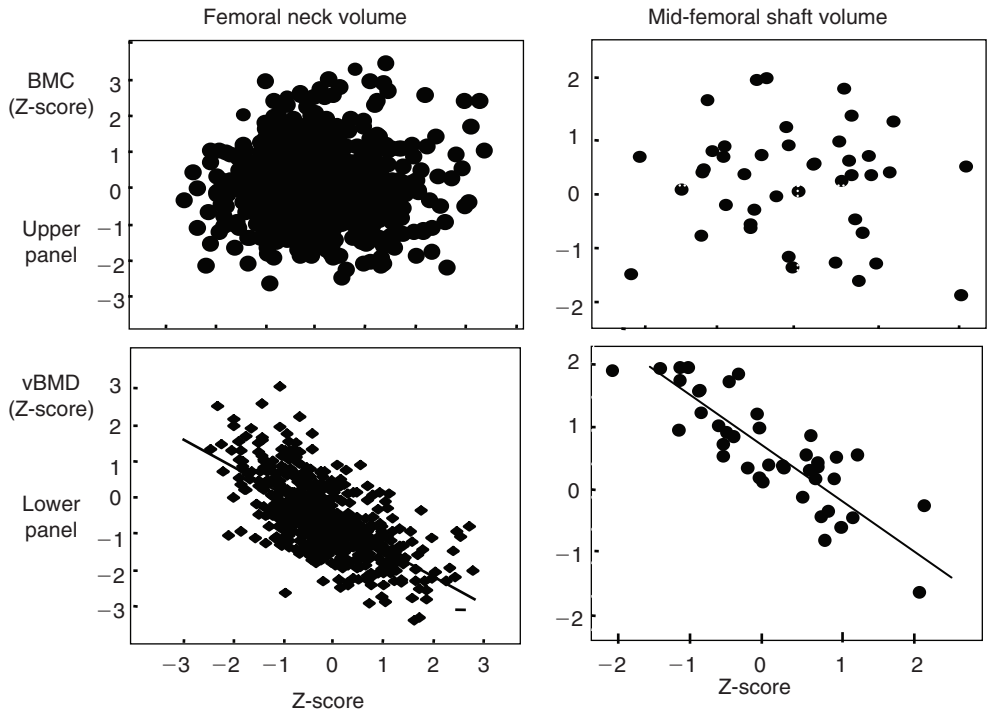

FIGURE 3 Upper panels: There is no association between the bone mineral content (BMC) Z-score and the volume of a femoral neck (FN) or femoral midfemoral shaft (FS) cross-sectional slice (including marrow volume). Lower panels: Larger cross-sections are assembled with relatively less mass and so have a lower volumetric apparent bone mineral density (vBMD). ("Apparent" refers to the vBMD of the whole cross-section, bone plus marrow areas.) Adapted from Zebaze *et al.* (2007).

Diversity in Bone Size, Shape, and the Spatial Distribution of its Mass

Long bones are not drinking straws with the same dimensions throughout their length; long bones do not have a single cross-sectional diameter, the same cortical thickness or marrow cavity diameter. Group means obscure variance – the diversity in structure and mass distribution so critical to determining diversity in bone strength. Bone strength and lightness are also achieved by altering bone shape. Diameters of a cross-section differ at each degree around the periosteal perimeter creating differences in the external shape of the cross-section. Differences in the medullary diameters at corresponding points around the endocortical perimeter determine the shape of the marrow cavity and the proximity of these two envelopes, which in turn then determine cortical thicknesses around the perimeter of the cross-section and the distance the cortical mass is placed from the neutral axis (Zebaze *et al.*, 2007).

This diversity in bone size, shape, and mass distribution is the result of differing degrees of focal bone formation at each point around the periosteal perimeter and resorption at the corresponding point on the endocortical surface during growth. Bone strength is optimized, not by using a greater net amount of mass, but by strategically modifying bone size, shape, and the distribution of mass using the minimum net amount of bone needed to do so.

For example, total cross-sectional area of the femoral neck is greatest adjacent to the shaft of the femur and smaller nearer the femoral head but the amount of bone in each cross-section is no different (Fig. 4). What differs is the way this bone is distributed in space as cortical and trabecular bone. Adjacent to the femoral shaft, the femoral neck cross-section is elliptical with long axis in the superoinferior direction. The marrow cavity shape follows the external shape, but not identically; the greater periosteal apposition superiorly and inferiorly relative to mediolaterally produces the elliptical shape. Differences in periosteal

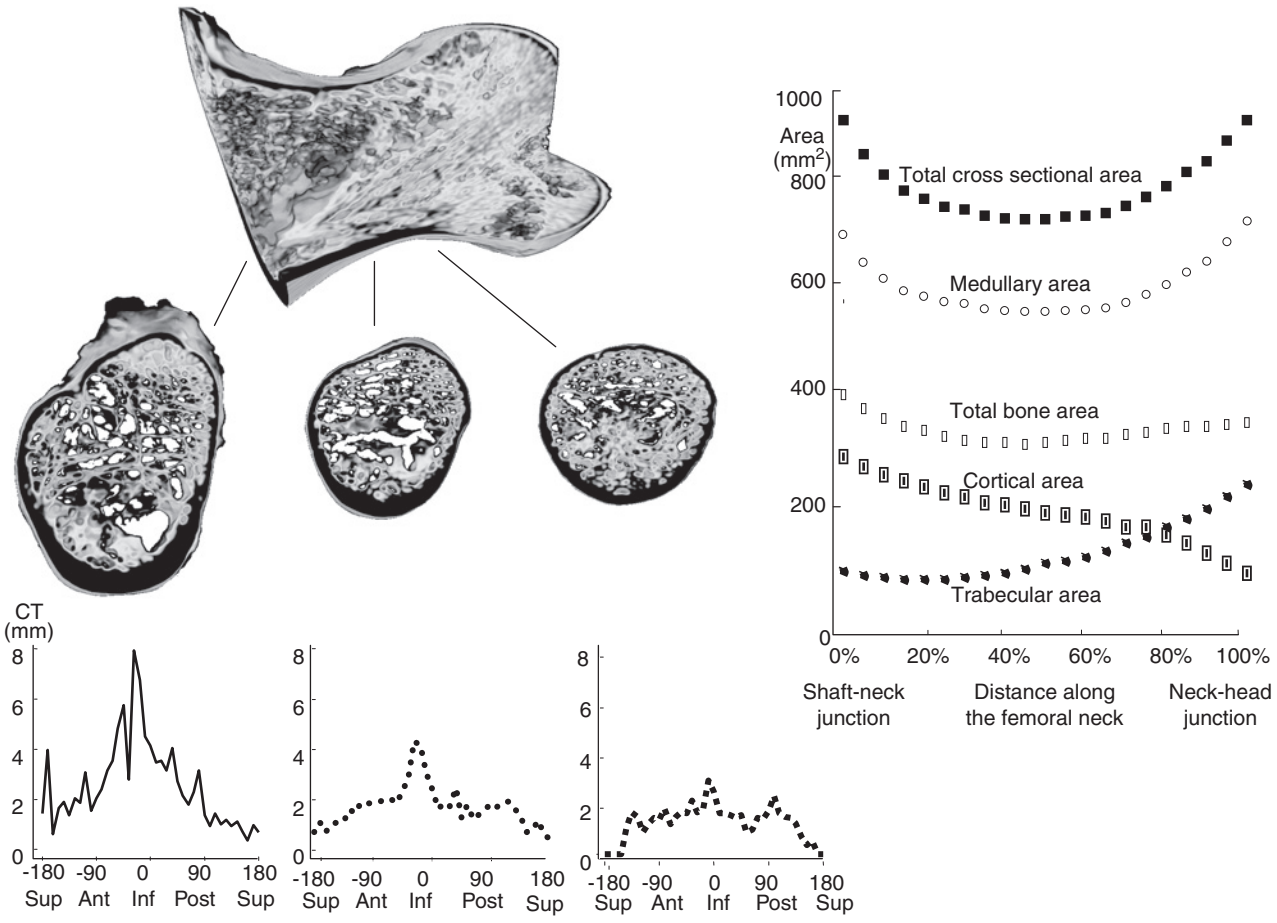

FIGURE 4 Femoral neck (FN) size and shape varies along its length. A similar amount of bone material is used to assemble each cross-section despite each cross-section varying in total cross-sectional area (CSA), shape, and proportions of cortical and trabecular bone. Adjacent to the femoral shaft the FN shape is elliptical and the bone is mainly cortical with varying cortical thickness (CT) at each point around the perimeter. At the mid-FN and adjacent to the femoral head the shape is more circular, there is more trabecular bone, reciprocally less cortical bone, which is similar in thickness around the perimeters. Adapted from Zebaze *et al.* (2007).

apposition and endocortical resorption produce a thicker cortex inferiorly and a thinner cortex superiorly (Zebaze *et al.,* 2007).

The bone in the cross-section at the junction of the femoral neck with the femoral shaft is largely cortical. Moving proximally, femoral neck shape becomes more circular reflecting similar degrees of periosteal apposition around the perimeter and the bone mass is distributed progressively more as trabecular and less cortical bone while cortical thickness is similar around the perimeter (as can be seen by the similar distribution profile in the lower part of Fig. 4).

The relative contributions of genetic factors and loading circumstances to this diverse structural organization is uncertain but modeling, by deposition bone, and remodeling by removing bone, assemble very different structures along the length of the femoral neck to accommodate differing loading patterns using similar net amounts of material.

This principle of optimizing strength and minimizing mass is illustrated in a prospective study of growth of a tibial cross-section assessed using quantitative computed tomography (Wang *et al.,* 2005; Wang *et al.,* 2007). In prepubertal girls, tibial cross-sectional shape was already elliptical at age 10. During two years, focal periosteal apposition increased the ellipticity by adding twice the amount of bone anteriorly and posteriorly than added medially and laterally. Consequently, estimates of bending strength increased more in the anteroposterior (Imax) than mediolateral direction (Imin) (Fig. 5). Marrow area changed little so more mass was distributed as a thicker cortex anteroposteriorly due to periosteal apposition without concurrent endocortical resorption. Resistance to bending increased by 44% along the principal axis (Imax) with a 22% increase in mass. If cortical thickness increased by the same amount of periosteal apposition at each point around the tibial perimeter, the amount of bone producing the same increase in bending resistance would be 205 mg, fourfold more than observed.

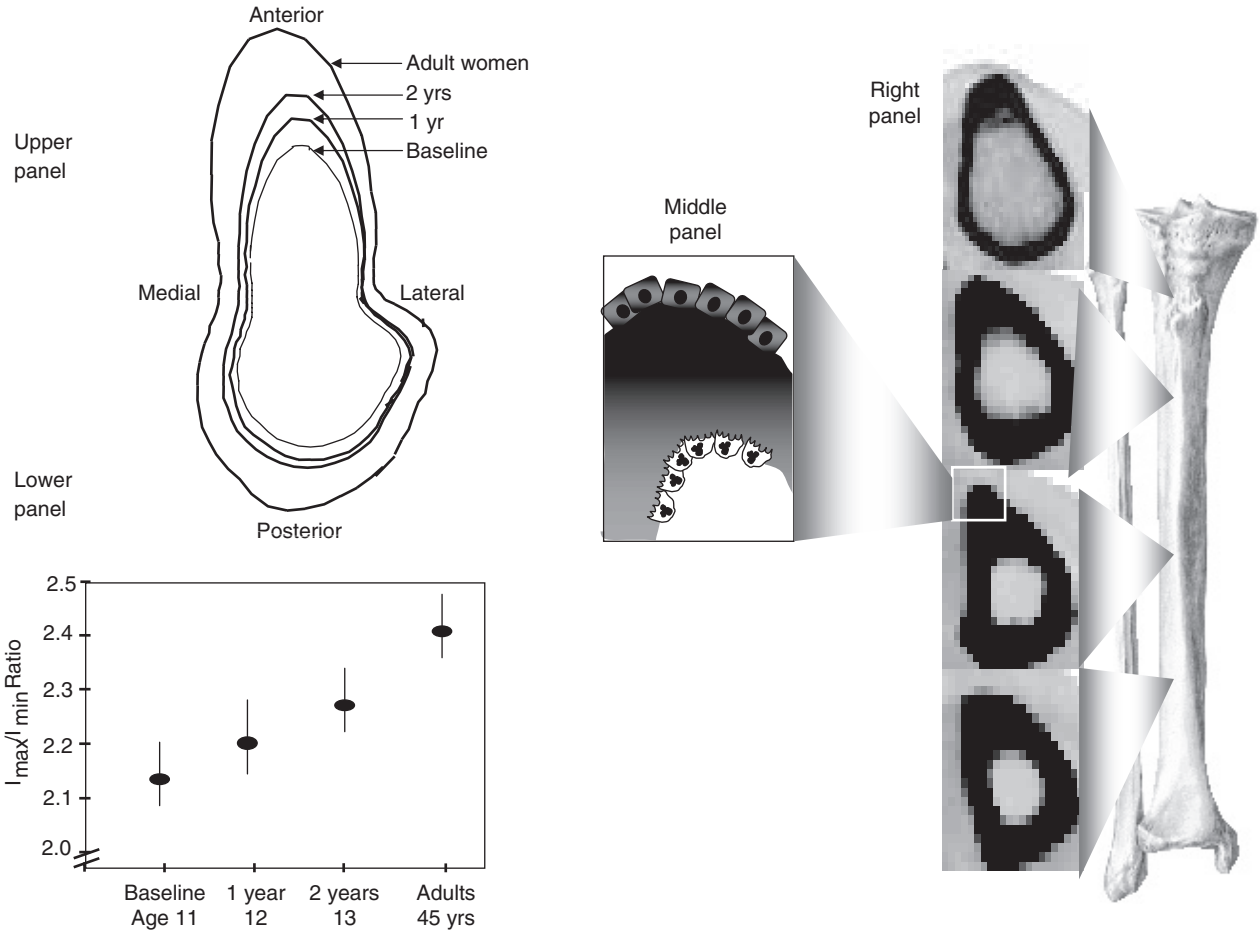

FIGURE 5 Left upper and lower panel: Bone mass distribution around the center of the tibial cross-section. More bone is deposited anteriorly and posteriorly than medially and laterally during two years of growth, increasing the ellipticity of the cross-section. Bending resistance increases more along the anteroposterior axis (Imax) than mediolateral axis (Imin) as reflected in the increasing ratio. Middle and right panel: Diagram depicting periosteal apposition and endocortical resorption modifying cortical thickness. Shape of the tibial cross-sections varies along the length of the tibial shaft. Adapted from Wang *et al.* (2007).

It is also intuitive that a bone with a larger cross-sectional area must be constructed with more periosteal bone than a smaller cross-section. The contrary was observed. During two years, the absolute amount of bone deposited on the periosteal surface of the tibial cross-section was similar in children with baseline tibial total cross-sectional area in the upper, middle, and lower tertile at age 10. Thus, larger cross-sections were assembled with less mass *relative* to their starting cross-sectional size avoiding bulk, and smaller cross-sections were assembled with more mass *relative* to their starting total cross-sectional size offsetting the fragility associated with slenderness.

Deposition of similar amounts of bone on the periosteal surface of larger and smaller cross-sections (and so less in relative terms on the former and more on the latter) was possible because the differences in bone size were established early, probably in utero (see later discussion). Consequently, the deposition of the same amount of bone on the periosteal surface of an already larger cross-section confers more bending resistance than deposition of the same amount of bone on a smaller cross-section because resistance to bending is proportional to the fourth power of the distance from the neutral axis (Ruff and Hayes, 1988).

This ability of bone to increase its strength in response to loading by adapting its design rather than increasing its mass is convincingly documented in racket sports. During growth, greater loading of the playing arm achieves greater bone strength by modifying its external size, shape, and the spatial distribution of its internal architecture. Focal periosteal apposition and endocortical resorption at some locations but endocortical bone formation at others changes the distribution of bone in space without a net change in its mass to accommodate loading patterns so that vBMD does not change; bending strength increases without increasing bulk, the latter hardly conducive to a good forehand volley (Haapsalo *et al.,* 2000; Bass *et al.,* 2002).

Trait Variances in Adulthood Originate Before Puberty

Although adults have larger skeletons than children, differences in bone size and mass in adult life probably have their origins established early in life. In a 3-year prospective study of growth in 40 boys and girls, Loro *et al.* report that the variance at Tanner stage 2 (prepuberty) in vertebral cross-sectional area and volumetric trabecular BMD, femoral shaft cross-sectional area (CSA) and cortical area was no less than at Tanner stage 5 (maturity); 60–90% of the variance at maturity was accounted for by the variance present before puberty. Thus, the magnitude of trait variances (dispersion around the age-specific mean) is largely established before puberty (Loro *et al.,* 2000).

The ranking of individual values at Tanner stage 2 was unchanged during 3 years in girls (Fig. 6). These traits tracked so that an individual with a large vertebral or femoral shaft cross-section, or higher vertebral vBMD or femoral cortical area before puberty retained this position at maturity. The regression lines for each of the quartiles did not cross during three years. Similar observations were made in boys (not shown).

Similar observations have been reported using peripheral computed tomography of the tibia in 258 girls. The magnitude of variance at ages 10–13 did not differ from that two years later, and did not differ from that of their premenopausal mothers (Wang *et al.,* 2007). Likewise, Garn *et al.* monitored 744 women and men during 25 years. About 90% of the variance in cortical thickness in adulthood was accounted for by variance at completion of growth 25 years earlier (Garn *et al.,* 1992). Emaus *et al.* reported distal and ultra distal radius size and mass tracked during 6.5 years follow-up of 5,366 women and men ages 45–84 (Emaus *et al.,* 2005; Emaus *et al.,* 2006).

Finding that the magnitude of the trait variances at maturity is no different from the magnitude of their variances before puberty suggests that growth in larger and smaller bones occurs at the same rate (Wang *et al.,* 2007). (If larger bones deposit more bone during growth than smaller bones, variance will increase.) In addition, the constant variance and tracking also suggests that environmental factors are likely to contribute little to total variance of a trait in the population.

If variance is established before puberty, when is growth more rapid in some individuals than others to give rise to these large variances in bone size and mass (1 SD = ~10% of the mean)? Do bones from individual to individual begin by being the same size then some grow more rapidly (deposit more bone per unit time than others) to form the upper tertile of a trait while others grow more slowly forming the middle and lower tertile?

The answer to this question is unknown. In infants and children between ages 1 and 10, the variance in diaphyseal diameter and muscle diameter was established at 1–2 years of age (Maresh, 1961). In a cross-sectional study of 146 stillborn fetuses ages 20–41 weeks' gestation, the percentage of a femur, tibia, and humerus diaphyseal cross-section that was cortical area was about 80–90% at 20 weeks' gestation and remained so across the 20 weeks of intrauterine life, suggesting that as bone size increased during advancing intrauterine life, the proportion of bone within the cross-section remained constant and was established prior 20 weeks' gestation (Rodriguez *et al.,* 1992). By contrast, one cross-sectional study using three-dimensional ultrasound suggested variance in femoral volume doubled during intrauterine growth (Chang *et al.,* 2007).

The divergence of data points of graphic analyses of growth creating the impression of increasing variance may be more apparent than real because larger numbers differ by larger absolute amounts. Further studies are needed to define the magnitude to trait variances by sex and race and to define the genetic and environmental components of that variance.

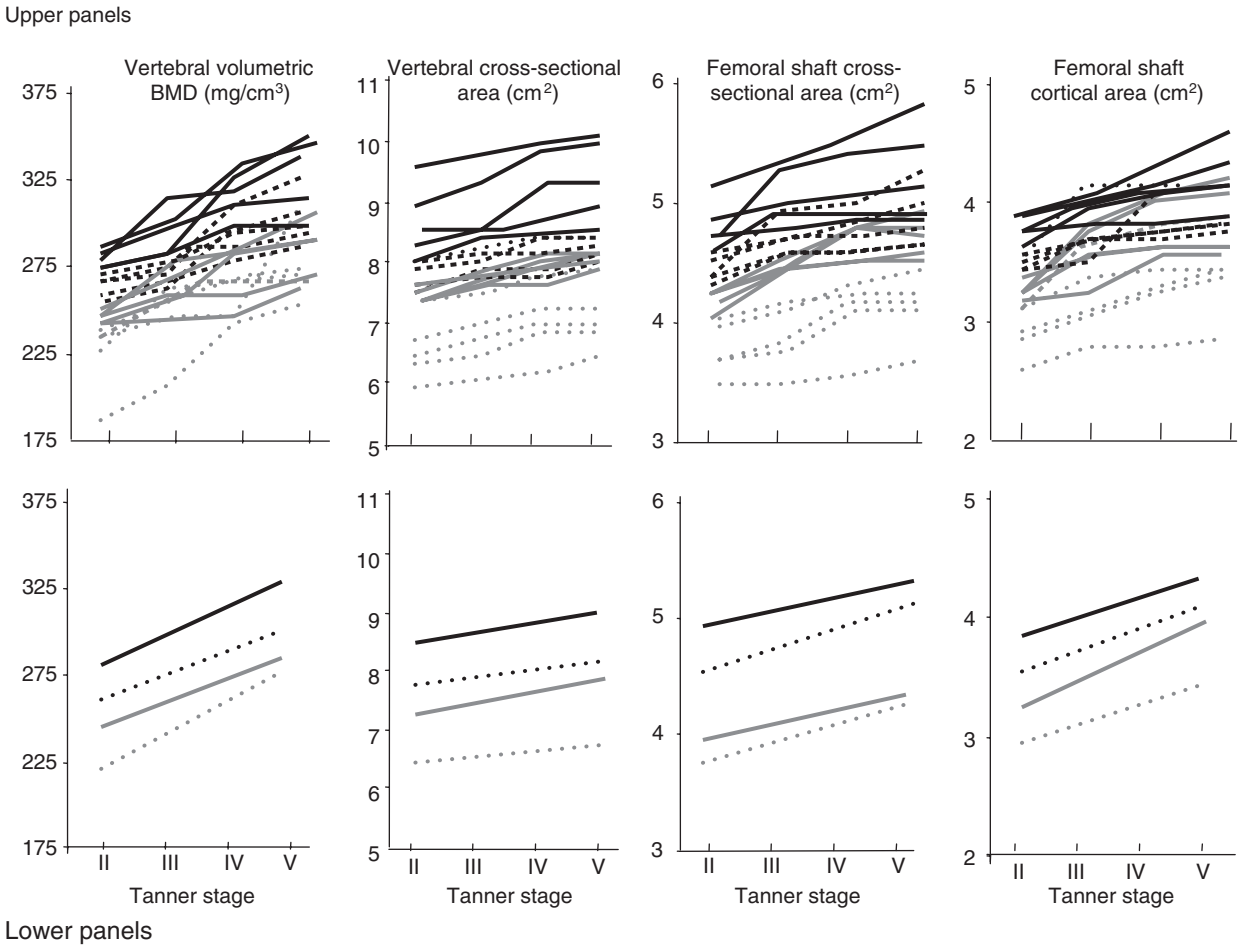

FIGURE 6 Upper panels: Variances in vertebral volumetric bone mineral density (vBMD) and cross-sectional area, femoral shaft total cross-sectional area and cortical area are established before puberty in girls. Individual values track retaining their percentile of origin during 3 years. Lower panels: The regression lines for each quartile do not overlap during 3 years. Adapted from Loro *et al.* (2000).

The obvious inference from the early establishment and constancy of trait variances is that genetic rather than environmental factors account for this variance. Studies in family members, twins, birth cohorts followed for many decades, and studies of fetal limb buds grown *in vitro* support this view (Murray and Huxley, 1925; Pocock *et al.,* 1987; Seeman *et al.,* 1996). However, this does not mean that traits *in an individual* are immutably fixed.

This flawed notion confuses variance in a population and the effect of environmental or disease on a trait in an individual. Muscle paralysis in utero, exercise during growth, or effects of disease in adulthood all have profound effects on bone structure in individuals (Bass *et al.,* 2002; Pitsillides, 2006). Lifestyle change can influence the population mean of a trait as documented many times by secular increases in height, a highly heritable trait (Bakwin, 1964; Meredith, 1978; Cameron *et al.,* 1982; Tanner *et al.,* 1982; Malina and Brown, 1987). However, under stable conditions, lifestyle differences within a population make only a small contribution to trait variances compared with genetic differences in that population.

Sex and Racial Differences in Axial and Appendicular Structure

For the vertebrae, increasing bone size by periosteal apposition builds a wider vertebral body in males than in females and in some races than in others (Seeman, 1998). Trabecular number per unit area is constant during growth. Therefore, individuals with a low trabecular number in young adulthood are likely to have had lower trabecular numbers in childhood (Parfitt *et al.,* 2000). The age-related increase in trabecular density is the result of increased thickness of existing trabeculae. Before puberty there is no difference in trabecular density in boys and girls of either Caucasian or African American origin (Gilsanz *et al.,* 1988; Gilsanz *et al.,* 1991). This suggests that both vertebral body size and the mass within its periosteal envelope increase in proportion until Tanner stage 3 (Fig. 7).

At puberty, trabecular density increases by race and sex, but within a race there is no sex difference in trabecular density. This increase is probably the result of cessation of external growth in bone size but continued bone formation

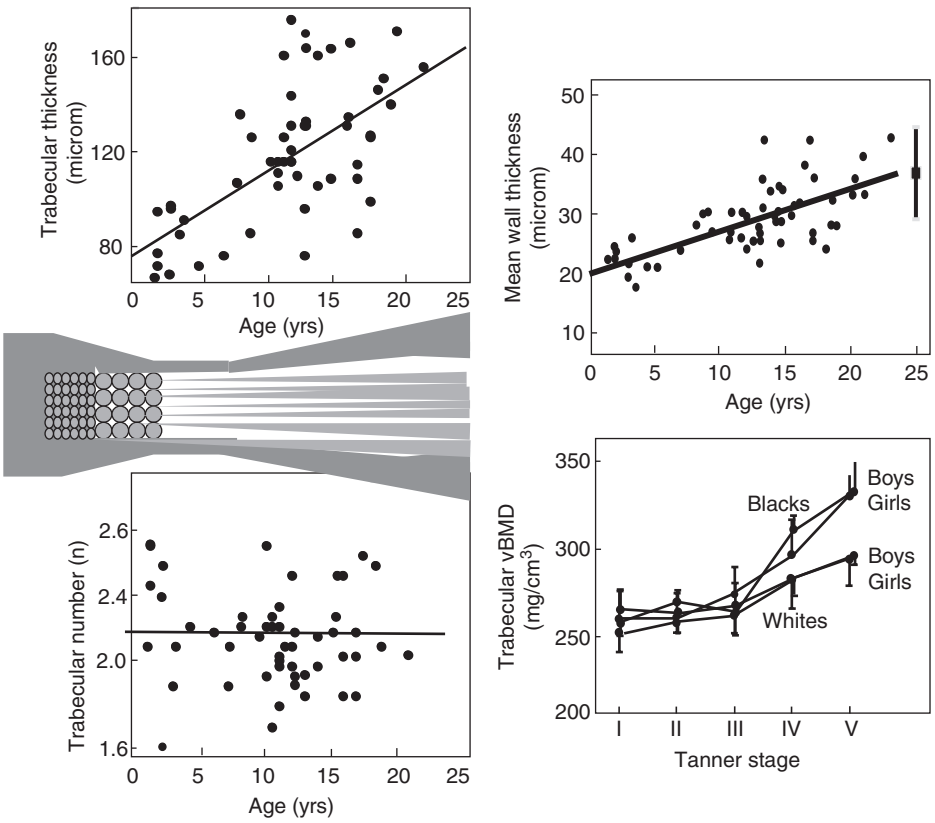

FIGURE 7 Trabecular volumetric bone mineral density (vBMD) increases with advancing age due an increase in trabecular thickness not numbers. This occurs by an increase in bone formation reflected in the increase in mean wall thickness. Adapted from Parfitt *et al.* (2000). Before puberty, trabecular vBMD is no different by sex or race, increases at Tanner stage 3 similarly by sex within a race but more greatly in African Americans than Caucasians. Adapted from Gilsanz *et al.* (1991).

on trabecular and endocortical envelopes resulting in more bone within the periosteal envelope of the bone – higher vBMD. Thus, growth does not build a "denser" vertebral body in males than females; it builds a bigger vertebral body in males. Strength of the vertebral body is greater in young males than females because of size differences. Within a sex, African Americans have a higher trabecular density than whites due to a greater increase in trabecular thickness (Han *et al.,* 1996). The mechanisms responsible for the racial dimorphism in trabecular density but resemblance in males and females within a race are yet to be defined. The greater trabecular thickness in African Americans accounts for the lower remodeling rate in adulthood because there is less surface available for remodeling (Han *et al.,* 1996).

Sex differences in appendicular growth are partly the result of differences in timing of puberty (Fig. 8). Before puberty there are already sex differences in diaphyseal diameter (Iuliano *et al.,* 2008). As long bones increase in length by endochondral apposition, periosteal apposition widens the lengthening long bone. Concurrent endocortical resorption excavates the marrow cavity but as periosteal apposition is greater than endocortical resorption, the cortex thickens. In females, earlier completion of longitudinal growth with epiphyseal fusion and earlier inhibition of periosteal apposition produces a smaller bone.

Bone length continues to increase in males and periosteal apposition increases cortical thickness. However, cortical thickness is similar in males and females because endocortical apposition in females contributes to final cortical thickness (Garn, 1970; Bass *et al.,* 1999). Cortical thickness is similar by race and sex. What differs is the position of the cortex in relationship to the long axis of the long bone (Wang *et al.,* 2005; Duan *et al.,* 2005). It is not clear whether the wider diaphysis in males than females is the result of accelerated periosteal apposition in males as commonly believed, or is the result of continued longitudinal growth in males as they enter puberty one to two years after females (Garn, 1970).

In summary, the cellular machinery of bone modeling and remodeling adapt bone size, shape, and mass distribution to its loading circumstances throughout the whole of growth ensuring that strength is optimized by depositing bone where it is needed and mass is minimized by removing bone from where it is not. The magnitude of the trait variances in adulthood are largely expressed in childhood. Traits track in their percentile of origin established at some time before puberty, if not in utero. Thus, differences in bone size and mass from individual to individual

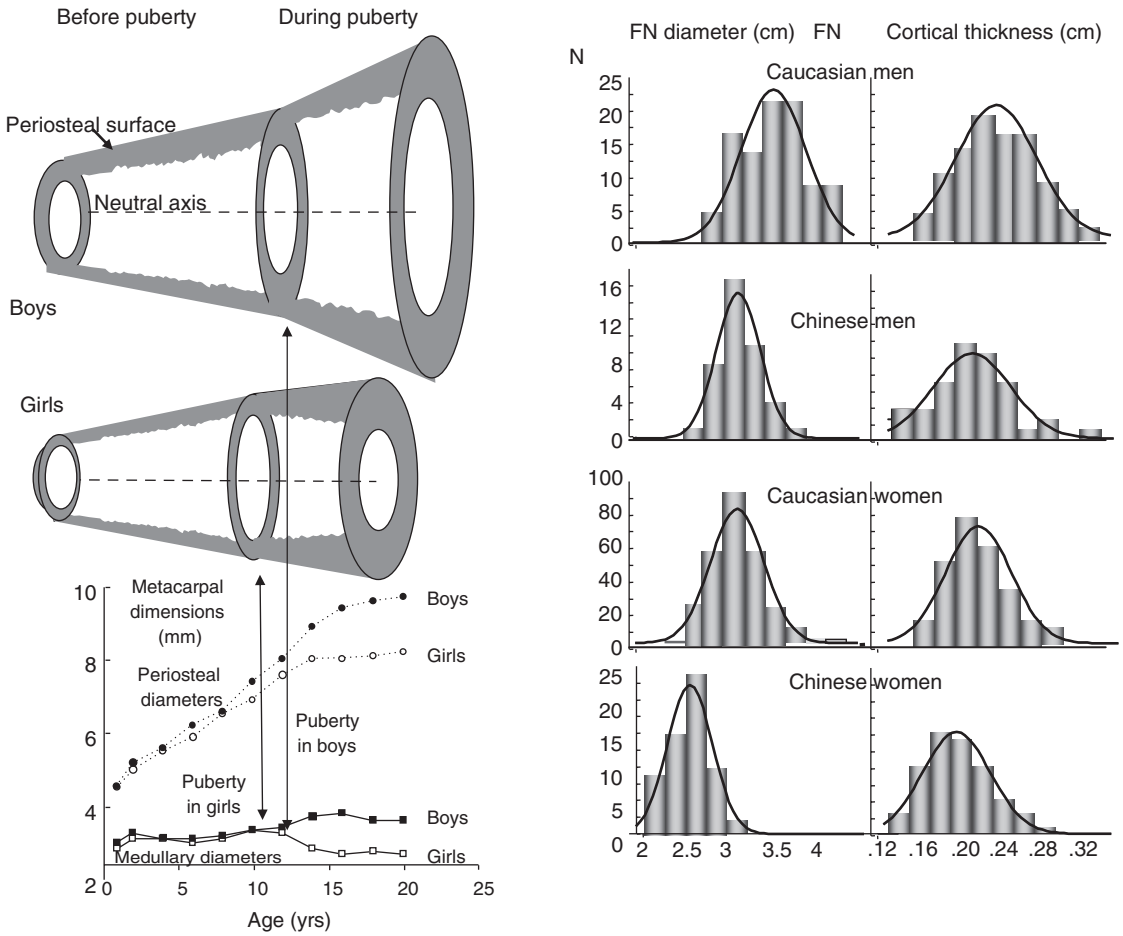

FIGURE 8 Long bone diameter is already greater in males than females before puberty. Growth in length and width continues longer in males because puberty occurs later. Endocortical apposition in females contributes to cortical thickness so that final cortical thickness is similar in males and females but displaced further radially in males. Adapted from Garn (1970). Distribution of femoral neck (FN) diameter differs by sex and race but femoral neck cortical thickness is similar by sex and race. E. Seeman with permission.

in adulthood are likely to be already evident early in life. This is obvious for cross-sectional size because periosteal apposition is minimal after completion of longitudinal growth. It is less obvious that the amount of bone within the periosteal envelope in adulthood is also largely established during growth (Zebaze *et al.,* 2007).

Variance in bone mass at completion of growth is an order of magnitude greater than variance in rates of bone loss during aging (1 SD = 10% versus 1%, respectively) (Parfitt, 1996). Thus, bone size, architecture, and mass attained during growth is likely to play an important role in determining the relevance of bone loss during advancing age (Hui *et al.,* 1999; Seeman *et al.,* 2001). For example, in children with larger tibial cross-sections, the advantage of assembling the larger bone with a relatively thinner cortex (to avoid bulk) may be a disadvantage when age-related bone loss occurs. Women with hip fractures and their daughters have larger femoral neck diameters and reduced vBMD (Filardi *et al.,* 2004). In smaller bones, the fragility of slenderness is offset by constructing them with more mass relative to their size as less endocortical resorption excavates a smaller marrow cavity, leaving a relatively thicker cortex. This balance may be compromised as bone loss produces cortical thinning and intracortical porosity which reduce compressive strength and resistance to bending.

BONE MODELING AND REMODELING IN ADULTHOOD AND THE EMERGENCE OF BONE FRAGILITY

The Purpose of Modeling and Remodeling in Adulthood – Maintenance of Bone Strength

The purpose of modeling and remodeling during growth is to achieve the skeleton's peak strength. The purpose of bone remodeling during adulthood is to maintain bone strength by removing damaged bone. *Bone, like roads, buildings, and bridges, develops fatigue damage during repeated loading but

only bone has a mechanism enabling it to detect the location and magnitude of the damage, to remove it, replace it with new bone, and thus to restore bone's material composition, micro- and macroarchitecture (Parfitt, 1996; Parfitt, 2002).

Bone resorption is not bad for bone unless it becomes excessive and untargeted. On the contrary, the resorptive phase of the remodeling cycle removes damaged bone and is essential to bone health. Indeed, prolonged suppression of remodeling using potent anti-resorptive therapy may result in microdamage accumulation, fractures, and reduced bone healing (Mashiba *et al.,* 2000; Odvina *et al.,* 2005). The formation phase of the remodeling cycle restores bone's structure provided that the volume of damaged bone removed is replaced by the same volume of normal bone. This process depends on the normal production, work, and life span of osteoclasts and osteoblasts, but the BMU is a *multicellular* unit and many cell types participate in the remodeling cascade.

The Pivotal Role of Osteocyte Death in Bone Remodeling

The osteocyte is one of these cells and is likely to play a pivotal role in bone modeling and remodeling. Osteocytes are the most numerous, longest-lived, and least studied cells of bone. There are about 10,000 cells per cubic millimeter and 50 processes per cell (Marotti *et al.,* 1990). These processes connect osteocytes with each other and with flattened lining cells on the endosteal surface. Thus, bone with its haversian and Volkmann canals and its lacunar-canalicular system is no less intricate in design than the hepatobiliary, bronchoalveolar, or glomerulotubular communication systems (Fig. 9, Panel 1). The dense lace-like network of osteocytes with their processes ensures that no part of bone is more than several microns from a lacuna containing its osteocyte suggesting that these cells are part of the machinery guarding the integrity of the composition and structure of bone (Parfitt, 2002).

Microcracks sever osteocyte processes in their canaliculi, producing osteocyte apoptosis (Hazenberg *et al.,* 2006) (Fig. 9, Panel 2). Apoptotic osteocytes may also be a form of damage, perhaps reducing the energy absorbing/dissipating capacity of bone when lacunae mineralize. Estrogen deficiency and corticosteroid therapy result in apoptosis (Manolagas, 2006). The increased remodeling rate in midlife in women may be partly the result of osteocyte death. Alternatively, or in addition, osteocyte apoptosis can produce damage to surrounding mineralized matrix producing bone fragility (independent of bone loss). Corticosteroid-treated mice have large osteocyte lacunae surrounded by matrix with a 40% reduction in mineral and reduced elastic modulus (Lane *et al.,* 2006). Genetic ablation of osteocytes produces bone fragility and failed mechanotransduction (Tatsumi *et al.,* 2007). Prevention of osteocyte death may be an attractive therapeutic target if they are damage or produce damage (Keller and Kneissel, 2005; Manolagas, 2006). Fragility can be prevented using anti-apoptotic agents (O'Brien *et al.,* 2004; Manolagas, 2006).

Whether apoptotic osteocytes are a consequence of damage, are the damage itself, or produce matrix damage, the number of dead osteocytes provides the topographical information needed to identify the location and size of damage (Verborgt *et al.,* 2000; Taylor 1997; Schaffler and Majeska, 2005) (Fig. 9, Panel 3). Osteocyte apoptosis is likely to be one of the first events signaling the need for remodeling. It precedes osteoclastogenesis (Clark *et al.,* 2005). *In vivo*, osteocyte apoptosis occurs within three days of immobilization and is followed within two weeks by osteoclastogenesis (Aguirre *et al.,* 2006). *In vitro*, death of the osteocyte-like MLO-Y4 cells induced by scratching results in the formation of TRACP positive (osteoclast-like) cells along the scratching path (Kurata *et al.*, 2006).

Thus, just as the spider knows the location and size of its wriggling prey by signals sent along its vibrating web, the need for reparative remodeling is likely to be signaled by osteocyte death via their processes connected by gap junctions to flattened osteoblast lining the inner or endosteal surface of bone where remodeling takes place. The nature of the signal from the osteocyte remains unknown.

The Pivotal Role of the Bone Remodeling Canopy in Bone Remodeling

It is not yet feasible to study the life of a BMU *in vivo*, documenting its birth, daily work in resorption, and formation to its end as an ossified osteon or hemi-osteon; the "fossilized" record of that remodeling cycle. Inferences regarding the sequence of events and their molecular regulation must be made with trepidation because observations are based on histomorphometric "snapshots" and *in vitro* studies of cell systems.

Bone remodeling occurs on the endocortical, trabecular, and intracortical components of the endosteal envelope. The endocortical and trabecular surfaces are adjacent to marrow. The intracortical surface forms the wall of haversian canals. While remodeling occurs on these endosteal surfaces, damage occurs deep to them, within the matrix of osteons or the interstitial bone between osteons in the case of cortical bone or within hemi-osteons in the case of trabecular bone. So, information concerning the location and size of damage must reach these surfaces and cells involved in remodeling must reach the site of damage beneath the endosteal surface. This anatomical arrangement makes the flattened lining cells conduits transmitting the health status of the bone matrix to the bone marrow environment, which in turn is a source of the cells of the BMU, but not the only source.

Apoptotic osteocytes signal the location and size of the damage burden to the flattened lining cells of the endosteal

Central regulation of bone remodeling and the role of remodeling in energy metabolism will not be discussed (Ducy *et al.,* 2000; Lee *et al.,* 2007).

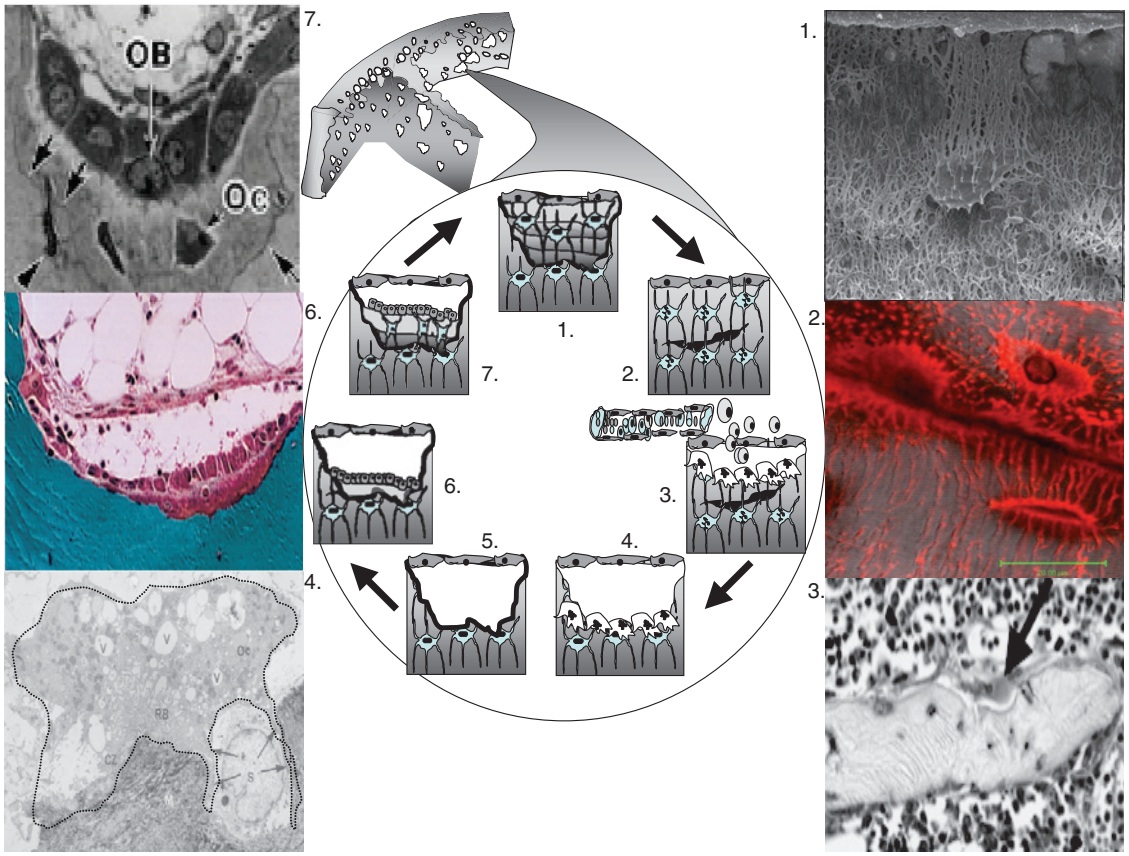

FIGURE 9 (1) Osteocytes are connected to each other and to lining cells on the endosteal surface adjacent to the marrow; (2) Damage to osteocytic processes by a microcrack produces osteocyte apoptosis. Courtesy J. Hazenberg *et al.* (2006); (3) The distribution of apoptotic osteocytes provides the topographical information needed to target osteoclasts to the damage. Courtesy M. Schaffler and R. Majeska (2005) (3) Collagenase from lining cells digests unmineralized collagen exposing mineralized bone and creates the bone remodeling cavity within which progenitors for osteoclastogenesis and osteoblastogenesis are delivered via the marrow or blood supply or locally (see text); (4) Osteoclasts (Oc) resorb bone and remove damage as well as phagocytosing osteocytes with its cytoplasmic extensions (arrows) inserted between lacunar wall and osteocyte (S). RB ruffled border, CZ clear zone, V vacuole. From Elmardi *et al.* (1990); (5) The reversal phase and formation of a cement line follows; (6) Osteoblasts deposit osteoid; and (7) Some osteoblasts are entombed in the osteoid they deposit and differentiate into osteocytes reconstructing the osteocytic canalicular network. From Suzuki *et al.* (2000). (See plate section)

surface leading to the formation of a bone remodeling compartment (BRC), which confines and targets remodeling to the damage minimizing removal of normal bone (Hauge *et al.,* 2001) (Fig. 9, cartoon and especially Panel 5). The regulatory steps between osteocyte apoptotic death and creation of the BRC are not known. Bone lining cells express collagenase mRNA (Fuller and Chambers, 1995). An early event creating the BRC may be collagenase digestion of unmineralized osteoid to expose mineralized bone, a requirement for osteoclastic bone resorption to proceed.

The flattened bone lining cells are probably osteoblasts. They express markers of the osteoblast lineage, particularly those forming the canopy over the BRC (Hauge *et al.,* 2001; Parfitt, 2001). These canopy cells also express markers for a range of growth factors and regulators of osteoclastogenesis such as RANKL suggesting that the canopy has a central role in the differentiation of precursor cells of marrow stromal origin, monocyte-macrophage origin, and vascular origins toward their respective osteoblast, osteoclast, or vascular phenotypes.

The Multidirectional Steps of the Remodeling Cycle

Although the two classical events of remodeling – resorption of a volume of bone by osteoclasts and formation of a similar volume of bone by osteoblasts occur sequentially (Hattner *et al.,* 1965), the cellular and molecular regulatory events leading to these two fully differentiated functions may not be sequential. Some may be contemporaneous and multidirectional; osteoblastogenesis and its regulators determine osteoclastogenesis and the volume of bone resorbed whereas osteoclastogenesis and the products of the resorbed matrix regulate osteoblastogenesis, while both may be regulated to some extent by osteocytes and its products (e.g., sclerostin). How this cellular and molecular traffic is orchestrated from beginning to end is far from clear.

Signaling from apoptotic osteocytes to cells in the canopy expressing the osteoblast phenotype may influence further differentiation toward osteoblast precursors expressing RANKL and fully differentiated osteoid-producing

osteoblasts. So even at this stage, regulation of osteoclastogenesis and osteoblastogenesis is occurring simultaneously through osteoblast precursors. In the MLO-Y4 cell line, damaged osteocyte-like cells have been reported to secrete M-CSF and RANKL (Kurata *et al.,* 2006). Whether this occurs in human subjects *in vivo* is not known but raises the possibility that osteocytes participate in the differentiation of monocyte-macrophage precursor cells toward the osteoclast lineage. Both osteoblast and osteoclast precursors circulate and so may arrive at the BRC via the circulation and via capillaries penetrating the canopy (Eghbai-Fatourechi *et al.,* 2005; Eghbai-Fatourechi *et al.,* 2007; Fujikawa *et al.,* 1996). The contribution of precursors from the canopy, the marrow via sinusoids or capillaries is not well-defined.

Angiogenesis is essential to bone remodeling. Osteoprogenitor cells are associated with vascular structures in the marrow and several studies suggest there may be common progenitors giving rise to cells forming the blood vessel and the perivascular cells that can differentiate toward cells of multiple lineages (Doherty *et al.,* 1998; Howson *et al.,* 2005; Sacchetti *et al.,* 2007; Matsumoto *et al.,* 2006; Kholsa, 2007; Otsura *et al.,* 2007; Khosla *et al.,* 2008).

Once differentiated, teams of osteoclasts resorb a volume of damaged bone but little is known of the factors determining the volume of bone resorbed, particularly how resorption stops after the damaged region has been resorbed. Osteoclasts phagocytose osteocytes and this may be one way the signal for resorption is removed (Fig. 9, Panel 4).

Products from the osteoclasts independent of their resorption activity, and products from the resorbed matrix partly regulate osteoblastogenesis and bone formation (Suda *et al.,* 1999; Martin and Sims, 2005; Lorenzo, 2000). In addition, products from the osteocyte may contribute to regulation of bone formation. For example, sclerostin is secreted by osteocytes and perhaps other cells as well. It is a product of the ScleroSteosis (SOST) gene and inhibits bone formation. Its inhibition is permissive to bone formation. Whether osteoblast precursors are generated before resorption has occurred, either from the canopy, or by products of the osteoclast before it started matrix resorption is not known. If so, these cells form preemptive teams of cells ready to deposit bone, die, become lining cells or osteocytes depending on later signals from osteoclasts, the resorbed matrix or products of the osteocyte such as sclerostin or cell–cell contact (Zhao *et al.,* 2006).

After the reversal phase, osteoblasts deposit osteoid partly or completely filling the trench cross-section (establishing the size of the negative BMU balance in that cross-section) and forming the lamellae that then undergo primary and secondary mineralization. In a given cross-section, how the osteoblasts change polarity to produce the differently orientated collagen fibers from lamella to lamella is not known. Most osteoblasts die, others become lining cells whereas others become entombed in the osteoid they formed to become osteocytes which communicate with each other to "rewire" the osteocytic canalicular communicating system for later mechanotransduction, damage detection, and repair (Han *et al.,* 2004).

In summary, bone remodeling may not be exclusively damage-driven but if it is, the osteocyte appears to play a pivotal role in initiating this remodeling cycle and perhaps participating in the regulation of the volumes of bone ultimately resorbed and formed by the BMU. Many of the advances that have taken place raise more questions than they answer. Some very fundamental questions concern the role of remodeling in intermediary metabolism, the link between central control of remodeling and regulation of remodeling for regional structural adaptation to loading and focal damage removal.

Even the question of what is "damage" betrays many areas in need of exploration. Damage at the nano- or microstructural level has not been comprehensively categorized in morphological terms so that the causes of damage, biomechanical effects, biochemical and structural means of detecting, signaling, and repairing different types of damage remain unstudied (Akkus *et al.,* 2004; Burr *et al.,* 1998; Danova *et al.,* 2003; Diab *et al.,* 2006; Diab and Vashisha, 2005; Garnero *et al.,* 2006; Landis, 2002; Ruppel *et al.,* 2006; Silva *et al.,* 2006; Taylor, 1997).

Age-Related Changes in Modeling and Remodeling Adulthood

Although bone can accommodate loading circumstance by adaptive modeling and remodeling during growth, this capacity diminishes because four age-related changes in the cellular machinery of bone modeling and remodeling compromise bone's material properties and structural design. Bone's ability to adapt to loading is impaired because each time a remodeling event occurs there is loss of bone and some structural decay (Seeman and Delmas, 2006).

Remodeling rate is rapid during growth because each remodeling event deposits only a small moiety of bone (Parfitt, 2002). As growth nears its "programmed" completion, rapid remodeling is no longer needed and remodeling rate slows. With the completion of longitudinal growth, the only requirement for bone formation is the repair of micro- and macrodamage so there is a decline in bone formation, a mechanism proposed to be responsible for bone fragility over 65 years ago (Albright *et al.,* 1941).

Thus, the first age-related change in this machinery is a reduction in bone formation at the cellular level by each BMU (Lips *et al.,* 1978; Vedi *et al.,* 1984) (Fig. 10). The second abnormality is also a reduction in bone formation but at the tissue level – bone modeling on the periosteal envelope slows precipitously after completion of

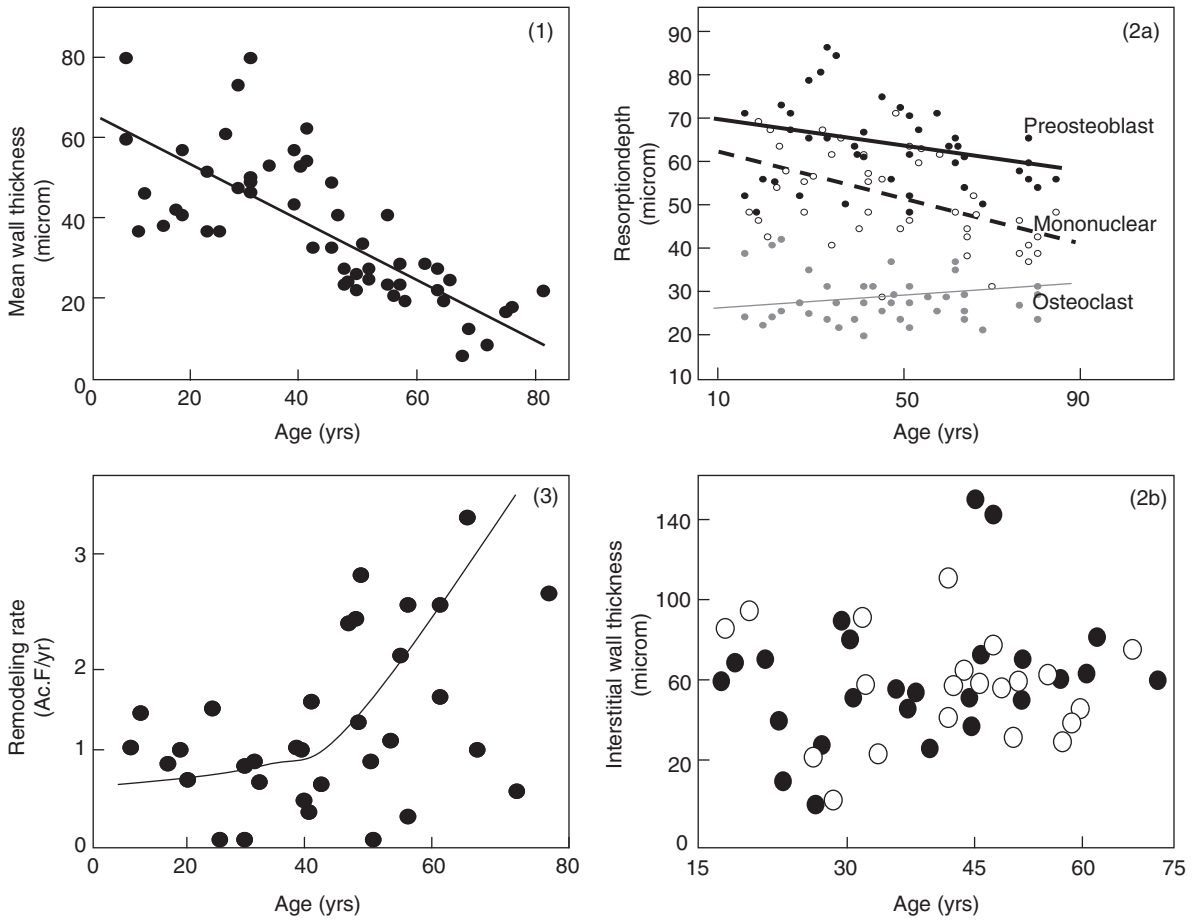

FIGURE 10 Endosteal bone loss is the result of: (1) a reduction in the volume of bone formed in each basic metabolic unit (BMU) reflected in a reduction in mean wall thickness with age. Adapted from Lips *et al.* (1978); (2) A fall or little change in the volume of bone resorbed in each BMU. This is reflected in (2a) as little change in erosion depth defined by preosteoblasts, mononuclear cells, or osteoclast surfaces (Adapted from Ericksen *et al.,* 1985) and (2b) and no change in interstitial wall thickness (females black symbols) Adapted from Vedi *et al.* (1984); and (3) Increased remodeling rate (activation frequency). Courtesy J. Compston.

longitudinal growth but continues slowly so that bone diameters enlarge, but no more than a few millimeters during the next 60 years.

The mechanisms responsible for the reduction in the volume of bone formed in each BMU are not well-defined but may include a reduction in stem cell precursors of osteoblasts, a reduction in differentiation of stem cells to the osteoblast lineage, reduced osteoid production of individual cells, and a reduction in the life span of these cells (Bonyadi *et al.,* 2003; Nishida *et al.,* 1999; Stenderup *et al.,* 2001; Oreffo *et al.,* 1998).

The third abnormality in remodeling is believed to be an increase in the volume of bone resorbed by the BMU but this may be confined to a brief period following sex hormone deficiency (Ericksen, 1986; Ericksen *et al.,* 1999; Manolagas, 2000; Compston *et al.,* 1995). The opposite may occur across the whole of life – the volume of bone resorbed by each BMU appears to decrease as reflected in a lower resorption cavity depth and an age-related increase, rather than decrease, in interstitial thickness (Croucher *et al.,* 1991; Ericksen *et al.,* 1999). (If resorption depth increased with age, interstitial wall thickness, the distance between cement lines of opposing hemi-osteons in trabecular bone, should decrease.)

The fourth age-related abnormality in the cellular machinery contributing to structural decay is an increase in the rate of bone remodeling after menopause. This is accompanied by worsening of the negative bone balance in each BMU as the volume of bone resorbed increases and the volume of bone formed decreases in the many more BMUs now remodeling bone on the three (endocortical, intracortical, and trabecular) components of its endosteal envelope (Manolagas, 2000).

Bone Loss During Young Adulthood

If the volume of bone resorbed decreases to the same degree as the decrease in the volume of bone formed by the BMU there will be no net negative BMU balance at the

completion of a remodeling cycle so remodeling events will not produce any permanent bone loss or structural decay. However, at some stage in midlife or early, there is a net negative bone balance as the volume of bone resorbed exceeds that formed (irrespective of the absolute decrease in both) and this negative BMU balance is the necessary and sufficient requirement for loss of bone from the skeleton, structural decay, and bone fragility.

There is evidence using noninvasive methods such as densitometry or computed tomography for a decline in bone mass in young adulthood in women and in men (Riggs *et al.,* 1986; Gilsanz *et al.,* 1987; Riggs *et al.,* 2007). Assuming the decline is not an artifact produced by an increase in marrow fat with age (Bolotin and Sievänen, 2001), this decline is likely to be the result of bone loss driven by a decline in bone formation. More definitive statements cannot be made due to lack of histomorphometric data in premenopausal women and young adult men.

Riggs *et al.* report a decline in trabecular volumetric density prior menopause in a 3-year prospective study of 553 women and men (Riggs *et al.,* 2007). Before age 50, women lose 37% and men 42% of the total trabecular bone lost across life, and 6% and 15% of lifetime cortical bone loss. The structural and biomechanical consequences are likely to be less than bone loss later in life because (1) remodeling rate is slow, (2) trabecular bone loss probably proceeds by reduced bone formation rather than increased bone resorption in the BMU, (3) bone loss proceeds by trabecular thinning rather than loss of connectivity so a given decrement in trabecular BMD produces less loss of strength than produced by loss of connectivity (van der Linden *et al.,* 2001), and (4) continued periosteal apposition partly offsets endocortical bone loss shifting the cortices radially maintaining cortical area and resistance to bending (Szulc *et al.,* 2006).

Bone Loss During Menopause and Advancing Age

Variance in the positive BMU balance on trabecular surfaces during growth is small compared with the variance in the rate of remodeling so that the rate of gain in bone mass is driven more by the remodeling rate. Similarly, the variance in the negative BMU balance during aging is small compared with the variance in the rate of remodeling so the rate of bone loss during menopause and aging is driven more by the remodeling rate.

Thus, the higher rate of bone remodeling is a most important determinant of bone loss and the increase in remodeling rate in midlife associated with estrogen deficiency is responsible for accelerated bone loss. Perimenopausal women with remodeling rates in the lowest quartile lose little bone (Szulc *et al.,* 2006). Estrogen deficiency also increases the volume of bone resorbed by each BMU by prolonging the life span of osteoclasts, and reduces the volume of bone formed by each BMU by reducing the life span of osteoblasts, thereby aggravating the negative BMU balance (Manolagas, 2000). Whether the changes in the life span of the cells is permanent or temporary is not known but the combination of a rapid remodeling and a more negative BMU balance than observed before menopause accelerates bone loss and structural decay after menopause.

Before menopause, remodeling is slow. The birth rate of new BMUs creating resorption cavities is matched by slow completion of previously created BMUs in their formation phase. At menopause, this steady state is perturbed by an increase in the birth rate of new BMUs on bone's endosteal envelope. The now many BMUs remove bone while the fewer BMUs created before menopause complete remodeling by depositing bone. This perturbation produces a net acceleration in bone loss and a rapid decline in BMD (Fig. 11).

This is the remodeling transient, a reversible loss of bone mass and bone mineral that is a consequence of the normal delay in onset and slower progression of the formation phase of the remodeling cycle in the many remodeling foci created after menopause (Parfitt, 1980). The temporary deficit in bone mass and mineral has three components: the excavation site that lacks osteoid and mineral, the osteoid that lacks mineral, and bone that has undergone primary but not secondary mineralization. Primary mineralization occurs rapidly, secondary mineralization, the slow enlargement of crystals of calcium hydroxy-apatite-like mineral takes many months to years to go to completion (Akkus *et al.,* 2003). At any time, there are osteons created in the immediate postmenopausal period and fewer, earlier created, osteons at various stages of completing secondary mineralization.

Bone loss slows in the three to five years following menopause, not because remodeling rate slows. It doesn't. The rate of bone loss slows because steady state is restored at the new higher remodeling rate. Now the large numbers of BMUs excavating resorption cavities are matched by completion of remodeling by bone formation the large numbers of BMUs created in early menopause. Bone loss continues at a faster rate than before menopause but at a slower rate than immediately after menopause because BMU balance is negative, perhaps more negative than before menopause producing a permanent deficit in bone mass and mineral mass. The higher the remodeling rate and the more negative the BMU balance, the greater the bone loss and structural decay. If the worsening BMU balance produced by changes in the life span of osteoclasts and osteoblasts is temporary, and the negative BMU balance lessens but persists, the rate of loss will also lessen, but it will persist because bone loss is driven by the high remodeling rate.

Remodeling occurs on bone surfaces (envelopes), much more on the endosteal envelope than the periosteal envelope (Balena *et al.,* 1992; Orwoll, 2003), and more on the

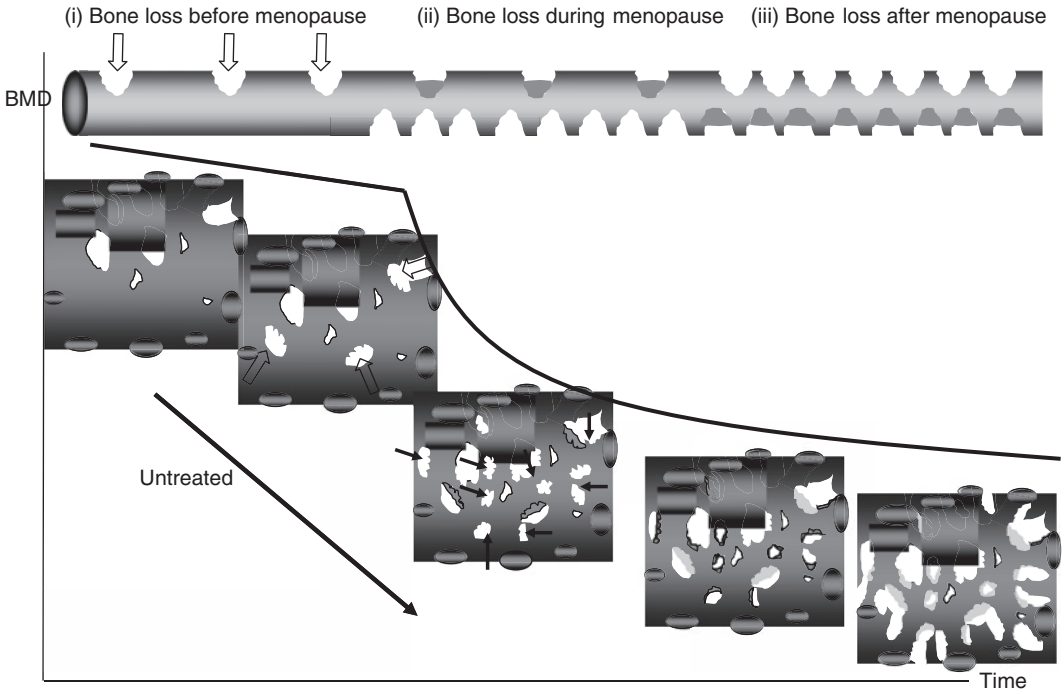

FIGURE 11 (i) Bone loss is slow before menopause because remodeling is slow; only a few sites on the trabecular surface remove bone (open arrows). (ii) Bone loss accelerates at menopause as remodeling rate increases. Now many basic multicellular units (BMUs) remove bone (black arrows) while the three BMUs initiated before menopause deposit bone. (iii) Bone loss after menopause slows because steady state is restored. The many BMUs removing bone at menopause are now in their formation phase but as many new BMUs are created and resorb bone. Bone is lost because each remodeling event removes bone from bone. E. Seeman with permission.

trabecular than endocortical and intracortical surfaces of the endosteal envelope. Trabecular bone has more surface per unit bone volume than cortical bone so that trabecular bone is more likely to be remodeled than cortical bone. Excavated resorption sites create stress "concentrators," that focus stresses to a single point (as a small cut in a test tube makes it easy to snap) (Hernandez *et al.,* 2006) (Fig. 12, upper panels). The high remodeling rate and negative BMU balance produces trabecular thinning and complete loss of trabeculae. Increased resorption depth is more likely to produce perforation and complete loss of trabeculae than either greater numbers of resorption cavities or reduced formation in the BMU in women (Parfitt, 1996). A 10% loss of trabecular density by perforation reduces strength more greatly than the same loss by trabecular thinning (Fig. 12, lower panel).

As remodeling continues, trabeculae are lost so the trabecular surface available for resorption decreases but remodeling on endocortical surface continues increasing the endocortical surface (like the folds of a curtain) (Parfitt, 1984; Brown *et al.,* 1987; Arlot *et al.,* 1990; Foldes *et al.,* 1991). Remodeling on the intracortical surface (haversian canals) increases intracortical porosity (Martin, 1984; Brockstedt *et al.,* 1993; Yeni *et al.,* 1997) (Fig. 13). Increased porosity due to increased numbers of pores and/or increased size of pores by coalescence of adjacent remodeling cavities increases the surface available for remodeling "trabecularizing" the cortex. Either total bone surface does not change (increasing in cortical bone, decreasing in trabecular bone) or increases (in regions of cortical bone only) so that late in life, bone loss is more cortical than trabecular in origin.

As age advances and remodeling continues at the same intensity due to estrogen deficiency and perhaps secondary hyperparathyroidism, the extent of coalescence of pores increases so the number of pores in cortical bone decreases but the total area of porosity increases, and perhaps more so in patients with hip fractures than controls (Bell *et al.,* 1999). Cortices porosity reduces the ability of bone to limit crack propagation so that bone cannot absorb the energy imparted by a fall and so it is released in the most undesirable way by fracturing (Martin, 1984; Yeni *et al.,* 1997). The continued remodeling at a similar intensity with its negative BMU balance, on the same amount or more surface, removes the same amount of bone from an ever-decreasing amount of bone accelerating the loss of bone and structural decay.

Rapid remodeling also modifies the material properties of bone increasing fracture risk. More densely mineralized bone is removed and replaced with younger, less densely mineralized bone, reducing stiffness (Boivin and Meunier, 2002; Boivin *et al.,* 2003). Increased remodeling impairs isomerization of collagen reducing bone strength (Viguet-Carrin *et al.,* 2006; Garnero *et al.*, 1996). Interstitial bone deep to surface remodeling becomes more densely mineralized and more highly cross linked with advanced glycation

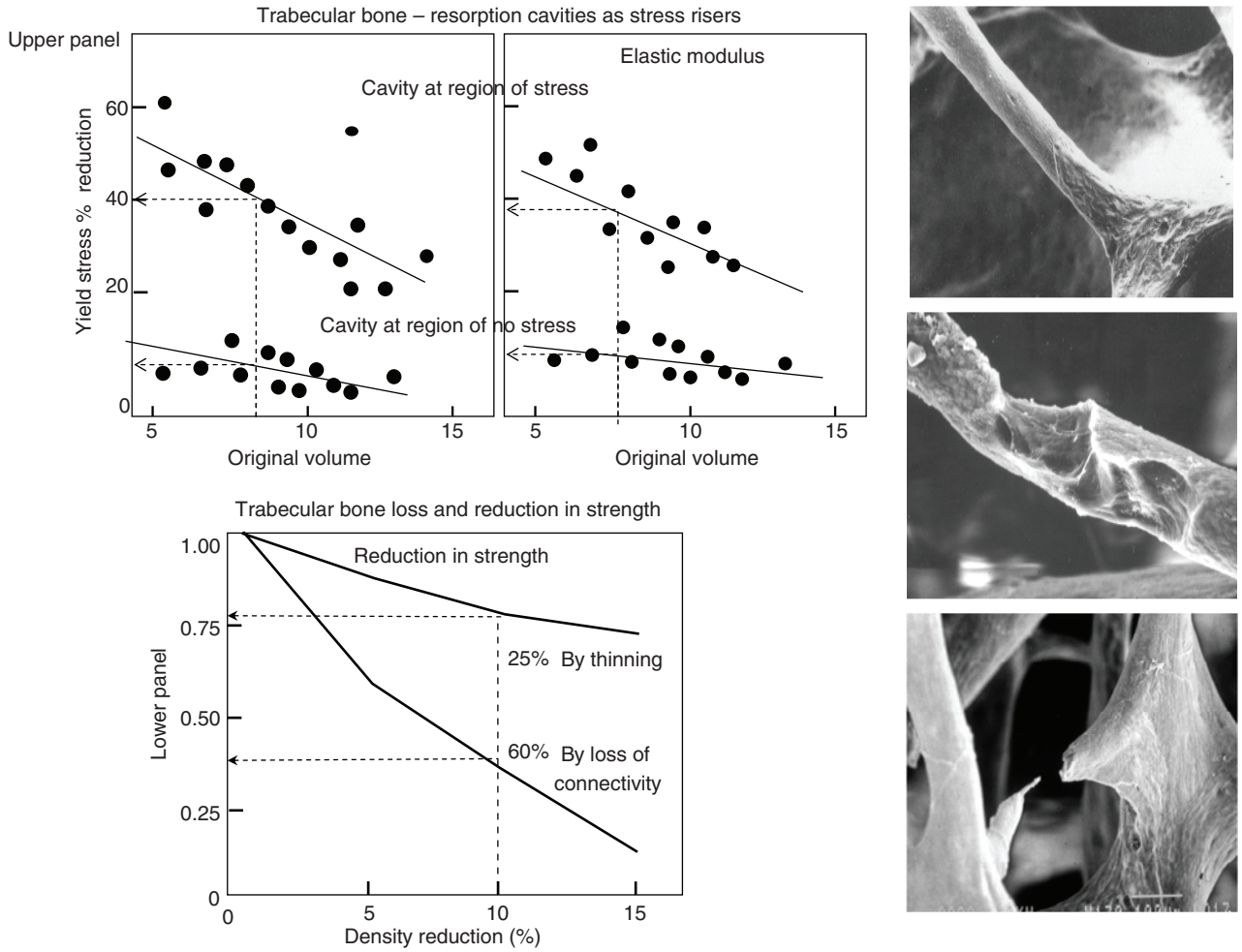

FIGURE 12 Upper panels: When resorption cavities occur in regions of stress on trabecular bone the decline in yield stress and elastic modulus is greater than produced by cavities in unstressed regions. Adapted from Hernandez *et al.* (2006). Lower panel: Reduction in strength produced by 10% deficit in trabecular density is greater when this deficit is produced by loss of trabecular connectivity than by thinning. Adapted from Van der Linden *et al.* (2001). Images show an intact trabecula, a resorption cavity, and loss of connectivity. Mosekilde and Mosekilde, 1990 With permission from the publisher.

products (AGEs) like pentosidine, both processes reducing bone toughness; it is easier for microcracks to travel through homogeneously mineralized bone and lengthen. Interstitial bone (between osteons) has reduced osteocyte numbers, accumulating microdamage (Bailey *et al.,* 1999; Banse *et al.,* 2002; Nalla *et al.,* 2004; Qui *et al.,* 2005; Yeni *et al.,* 1997).

Net Effects of Reduced Periosteal Bone Formation and Endosteal Bone Loss

The challenges regarding identifying the existence of periosteal apposition during adulthood, its site specificity, magnitude, and sex differences are considerable. In cross-sectional studies, secular changes in bone size may obscure or exaggerate periosteal apposition. These problems are not necessarily resolved by adjusting for height. Secular increases in stature occur in one or both sexes, in some races but not others and may occur in the skelton of the upper or lower body (Bakwin, 1964; Meredith, 1978; Cameron *et al.,* 1982; Tanner *et al.,* 1982; Malina and Brown, 1987). These secular trends can produce misleading inferences when increments or lack of increments in bone diameters are used as surrogates of periosteal apposition.

For example, in cross-sectional studies, absence of an increment in periosteal diameter across age may not mean periosteal apposition was absent. Earlier born individuals (the elderly in a cross-sectional sample) may have been shorter and had more slender bones than later born individuals (young normals in a cross-sectional sample). When periosteal apposition occurs, earlier born with more slender bones have an increase in bone diameter that comes to equal that in later born group (who have not yet had age-related periosteal apposition) leading to the flawed inference that there was no periosteal apposition in the cross-sectional sample.

When comparisons are made between sexes (or races) in cross-sectional studies, if the truth is that periosteal

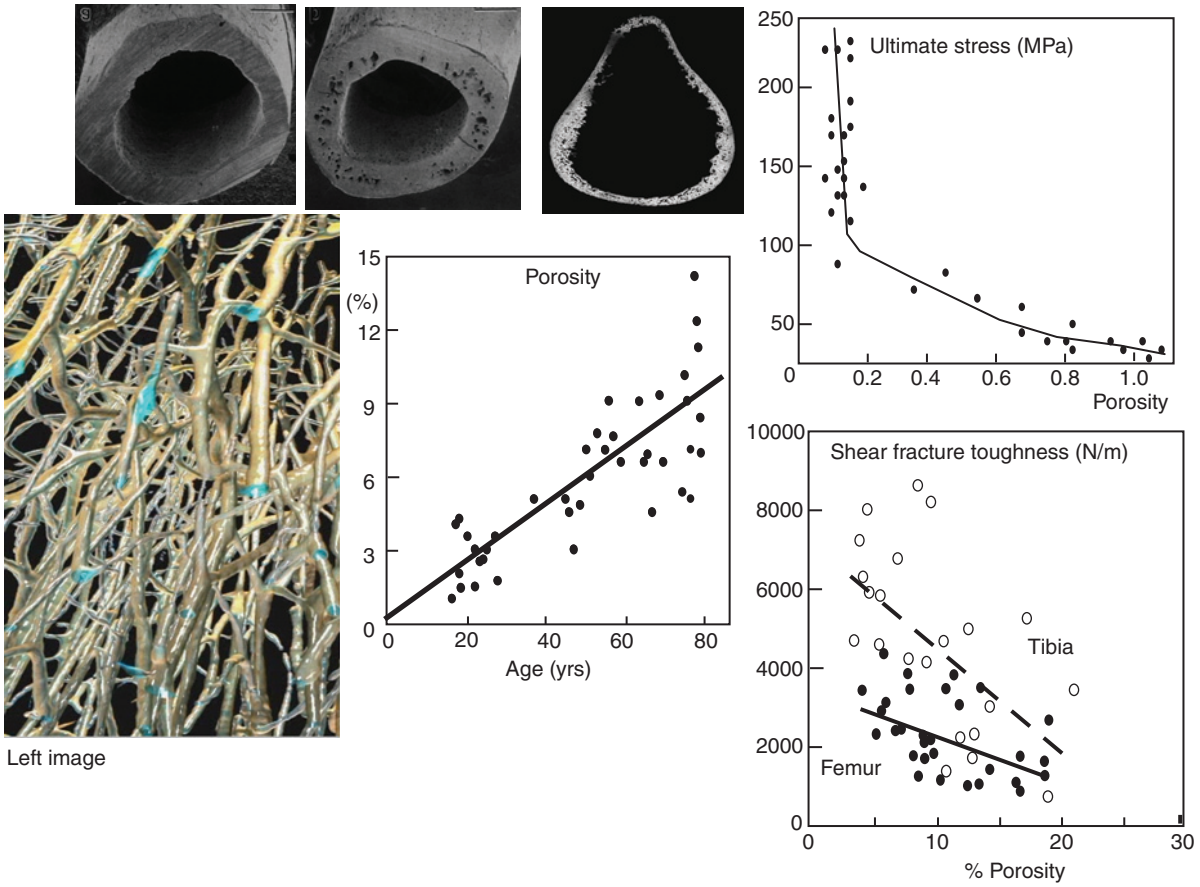

FIGURE 13 Cortical porosity increases as age advances (Brockstedt *et al.* 1993). This is associated with a decline in ultimate stress (adapted from Martin, 1984) and reduction in toughness (adapted from Yeni *et al.,* 1997). Upper images illustrate increasing porosity and thinning. Left image shows haversian canals in longitudinal section responsible for porosity in cross-section. Courtesy M. Knackstedt, Australian National University, Canberra. (See plate section)

apposition is greater in men than women but men have a secular increase in bone size and women do not, then the secular increase in men will blunt the increment in bone width across age in men and make it appear that the age-related increase in vertebral and femoral neck diameters (and so periosteal apposition) is similar in women and men. Longitudinal studies are also problematic because changes in periosteal apposition during aging are small (Balena *et al.,* 1992). The precision of methods to determine bone diameter, usually bone densitometry, and problems with edge detection when bone mineral density is changing limit the credibility of these measurements.

Periosteal apposition is believed to increase as an adaptive response to compensate for the loss of strength produced by endocortical bone loss, so there will be no *net* loss of bone, no cortical thinning, and no loss of bone strength (Alhborg *et al.*, 2003). In a 7-prospective study of over 600 women, Szulc *et al.* report that endocortical bone loss occurred in premenopausal women with concurrent periosteal apposition (Szulc *et al.,* 2006) (Fig. 14). As periosteal apposition was less than endocortical resorption, the cortices thinned but there was no *net* bone loss because the thinner cortex was now distributed around a larger perimeter conserving total bone mass. Moreover, resistance to bending increased despite bone loss and cortical thinning because this same amount of bone was now distributed further from the neutral axis. So bone mass alone is a poor predictor of strength because resistance to bending is determined by the spatial distribution of the bone.

Endocortical resorption increased during the perimenopausal period, yet periosteal apposition decreased – it did not increase as predicted if the notion that periosteal apposition is a compensatory mechanism is correct. The cortices thinned as periosteal apposition declined further. Nevertheless, bending strength remained unchanged – despite bone loss and cortical thinning because periosteal apposition was still sufficient to shift the thinning cortex outwards.

Bone fragility emerged only after menopause when accelerated in endocortical bone resorption and deceleration in periosteal apposition produce further cortical thinning. As periosteal apposition was now minimal, there was little outward displacement of the thinning cortex so cortical area now declined as did resistance to bending. Endocortical

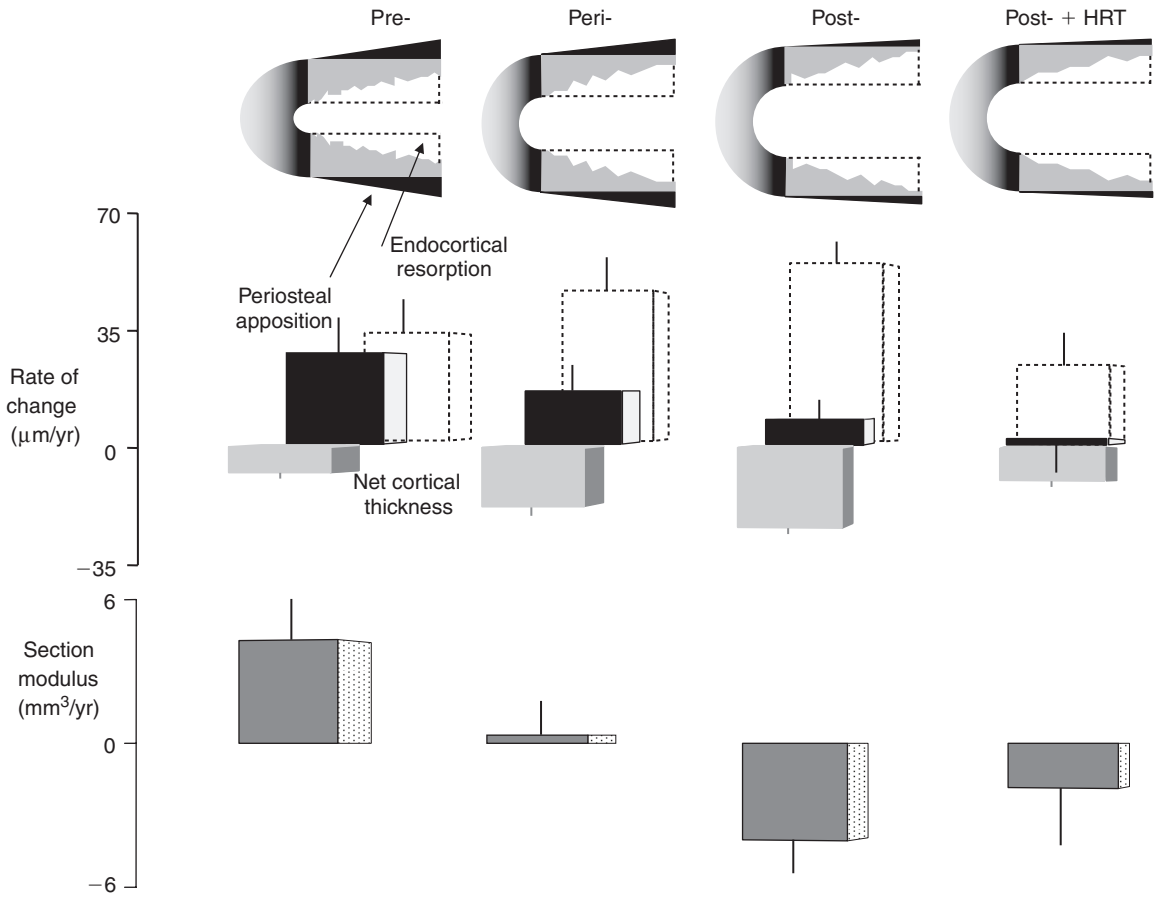

FIGURE 14 The amount of bone resorbed by endocortical resorption (open bar) increases with age. The amount deposited by periosteal apposition (black bar) decreases. The net effect is a decline in cortical thickness (grey bar). In premenopausal women, the thinner cortex is displaced radially increasing section modulus (Z). In perimenopausal women Z does not decrease despite cortical thinning because periosteal apposition still produces radial displacement. In postmenopausal women, Z decreases because endocortical resorption continues, periosteal apposition declines and little radial displacement occurs. In women treated with hormone replacement therapy (HRT), resorption is decreased with no effect on periosteal apposition. Z is less reduced than in untreated women. Adapted from Szulc *et al.,* 2006.

resorption was reduced but not abolished in women receiving hormone replacement therapy while periosteal apposition was no different to untreated women; cortical thinning was reduced and the resistance to bending occurred but less than in untreated women.

Periosteal envelope is regarded exclusively as a bone-forming surface. This is incorrect (Balena *et al.,* 1992). During growth, bone resorption is critical for the in-wasting that produces the fan-shaped metaphyses (Rauch *et al.,* 2001). Blizoites and colleagues report that bone resorption occurs in adult nonhuman primates (Blizoites *et al.,* 2006). Femur specimens from 16 intact adult male and female nonhuman primates showed that periosteal remodeling of the femoral neck in intact animals was slower than in cancellous bone but more rapid than at the femoral shaft. Gonadectomized females showed an increase in osteoclast number on the periosteal surface compared with intact controls. If these data are correct, adult skeletal dimensions may decrease in size as age advances.

Thus, even though the genius of bone biology Fuller Albright suggested over 65 years ago that osteoporosis was a disorder of reduced bone formation (Albright *et al.,* 1941), research into the pathogenesis of bone fragility during the last 40 years has focused on the role of increased bone resorption. During aging, both increasing endocortical bone resorption and reduced periosteal apposition cause *net* bone loss, alterations in the distribution of the remaining bone, and the emergence of the bone fragility. The cellular basis of the vigor of bone formation during growth and progressive decline in vigor during aging on the periosteal surface and within each BMU is yet to be defined.

Sex and Racial Differences in Trabecular and Cortical Bone Loss

A greater proportion of women than men sustain fragility fractures during their lifetime. The reasons for this sexual

dimorphism are not clear. Men have a larger skeleton than women do so that resistance to bending is greater in men than women. Bone loss in most, but not all, men is the result of a negative BMU balance produced by reduced formation rather than increased resorption by the BMUs, so trabecular bone loss occurs by thinning rather than loss of connectivity (Aaron *et al.,* 1987). Men do not have a midlife decline in sex hormones and increase in remodeling rate that drives structural decay produced by the negative BMU balance. Better preservation of trabecular bone in elderly men leaves more trabecular surfaces for remodeling to occur upon so trabecular bone loss continues longer in men (Aaron *et al.,* 1987). Net trabecular bone loss across age is only slightly greater in women than men (Riggs *et al.,* 2004), or is similar (Aaron *et al.,* 1987; Meunier *et al.,* 1990; Kalender *et al.,* 1989; Mosekilde and Mosekilde, 1990; Seeman, 1997; Seeman *et al.,* 2001). However, the same deficit in trabecular density produced by thinning (as occurs in men) produces less reduction in strength than produced by loss of connectivity (as occurs in women) (Van der Linden *et al.*, 2001).

Marrow cavity expansion occurs in both sexes but whether it is greater in women than men is uncertain (Riggs *et al.,* 2004). Cortical porosity increases less in men than in women because remodeling rate is lower in men and so crack propagation in cortical bone is probably better resisted in men than in women. Periosteal apposition is reported to be greater in men than in women in some (Duan *et al.,* 2001, Duan *et al.,* 2003, Duan *et al.,* 2005, Wang *et al.,* 2005, Seeman *et al.,* 2001) but not all studies (Riggs *et al.,* 2004).

Thus, methodological issues must temper the inferences that can be made regarding the basis of sexual dimorphism in bone strength (Seeman *et al.,* 2004). The absolute risk for fracture in women and men of the same age and BMD is similar (Kanis *et al.,* 2001; Kanis *et al.,* 2005). The lower fracture incidence in men than in women is likely to be the result of lower proportion of elderly men than elderly women having material and structural properties (cortical thinning, porosity, trabecular thinning, loss of connectivity, microdamage) below the critical level at which the loads on the bone are greater than the bone's net ability to tolerate them. Structural failure occurs less in men because the relationship between load and bone strength is better maintained in men than in women (Riggs *et al.,* 2006, Bouxsein *et al.,* 2006).

The Heterogeneous Material and Structural Basis of Bone Fragility in Patients with Fractures

Patients with fractures are grouped by having "one or more minimal trauma vertebral fractures," or sustaining a fall from "no greater than the standing position." However, the pathogenesis and structural basis of the bone fragility underlying the fractures is heterogeneous. Patients with vertebral fractures may have high, normal, or low remodeling rates (Brown *et al.,* 1984; Arlot *et al.,* 1990; Delmas, 2000). Some have a negative BMU balance due to reduced formation, increased resorption, or both, or no negative BMU balance at all (Ericksen *et al.,* 1990). Some patients with vertebral fractures have increased, whereas others have reduced, tissue mineral density (Ciarelli *et al.,* 2003) (Fig. 15). Some patients have reduced osteocyte density; others do not (Qui *et al.,* 2003; Qui *et al.,* 2005). Contemporary therapeutics gives no consideration to the underlying pathogenesis or structural abnormalities present in an individual. Whether anti-fracture efficacy can be improved from its current values of 50% for vertebral and hip fractures and 20% for nonvertebral fractures (Delmas, 2002) by defining the pathogenesis and structural basis in an individual remains uncertain, but it is worthy of exploration.

SUMMARY AND CONCLUSION

The purpose of modeling and remodeling during growth is to optimize bone strength by depositing bone where it is needed and to minimize mass by removing it from where it is not needed. Bone must be stiff – resistant to deformation, yet flexible – able to store energy in elastic deformation or to dissipate it. Otherwise, energy will be released by structural failure – fracture.

These paradoxical properties are achieved by bone's material composition and structural design. Material composition is similar among mammals so differences in bone strength in adulthood are largely the result of structural diversity. This diversity is already expressed before puberty. The magnitude of the variance in bone size and mass in prepubertal children is similar to that in their parents. Individuals with traits in the 5th, 50th, or 95th percentile in adulthood occupied these positions in early life because traits track along their percentile of origin. Long bones with a larger cross-section have a biomechanical advantage so the same periosteal apposition on a larger cross-section (i.e., less relative to size) confers greater stiffness than on a smaller cross-section. Endocortical resorption excavates a larger marrow cavity shifting the cortex radially, increasing stiffness and minimizing mass; larger bone cross-sections have a lower volumetric bone mineral density (vBMD). In slender bones, higher vBMD is the result of similar amounts of periosteal apposition (more relative to size) and less endocortical resorption, which excavates a smaller marrow leaving a relatively thicker cortex to offset the fragility of slenderness. Varying cellular activity around the periosteal and endocortical envelopes fashions the diverse shapes of adjacent cross-sections. Vertebral bodies are fashioned as a honeycomb of trabecular plates and void spaces conferring flexibility and lightness.

Modeling and remodeling are successful during growth, not adulthood. The purpose of modeling and remodeling during adulthood is to maintain bone strength by damage

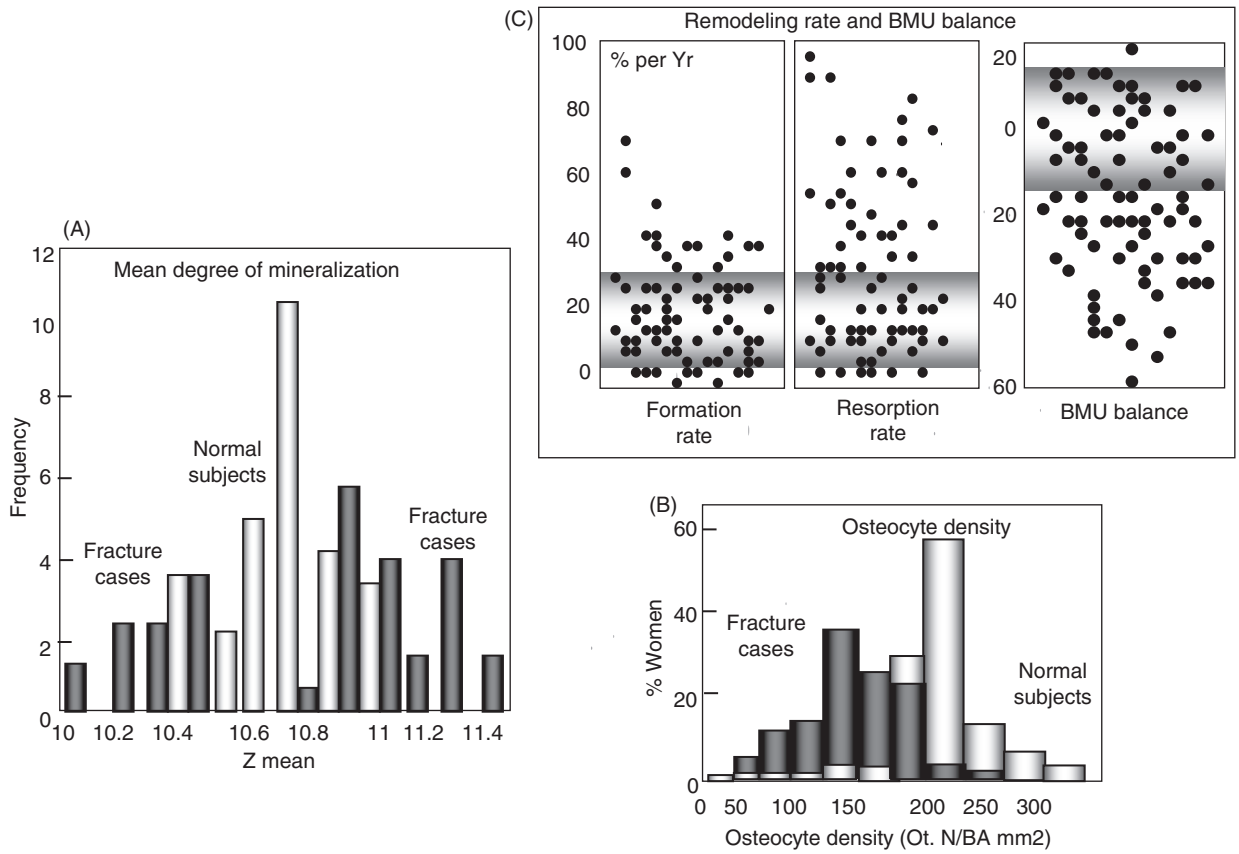

FIGURE 15 Bone fragility in patients with fractures has a heterogenous pathogenesis and structural basis. Patients have tissue mineral density in the upper or lower part of the normal distribution (adapted from Ciarelli *et al.,* 2003). Some have reduced or normal osteocyte density (adapted from Qui *et al.,* 2003). Formation and resorption rates may be lower normal or high bone balance in the basic multicellular level (BMU) may be normal or negative (adapted from Ericksen *et al.,* 1990).

repair but four age-related changes compromise bone's material composition and structure; a decline in periosteal bone formation, a decline in the volume of bone formed by each basic multicellular unit (BMU), continued resorption by each BMU, and high remodeling. Bone loss occurs in early adulthood but the structural and biomechanical consequences are modest because the negative BMU balance is driven by reduced bone formation not increased resorption, remodeling is slow and modest periosteal apposition offsets endocortical bone loss shifting the thinner cortex radially. After menopause, increased remodeling, worsening negative BMU balance, and a decline in periosteal apposition accelerate cortical thinning and porosity, trabecular thinning, and loss of connectivity. Interstitial bone, deep to surface remodeling, becomes more densely mineralized, has few osteocytes, greater collagen cross-linking, and accumulating microdamage. Late in life secondary hyperparathyroidism sustains high remodeling producing further cortical thinning and porosity. These age-related changes produce the material and structural abnormalities responsible for bone fragility.

Recent advances raise many questions concerning the uni-, bi- and multidirectional regulation and steps in remodeling, how resorption and formation phases are regulated and co-regulated, how osteocytogenesis occurs and the lacunar-canalicular system is reestablished for mechanotransduction and damage detection. Damage removal may not be the only reason bone remodels but is likely to be one of its main purposes in adulthood. However, the nature of "damage" has not been systematically defined and so questions remain concerning the determinants of damage production, its biomechanical consequences, and how different types of damage are signaled for repair. Thus, our understanding of why or how bones fail at the material and structural level remains incomplete. This is an essential direction of enquiry if we are to provide targeted approaches to drug therapy.

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