FUTURE DIRECTIONS IN MUSCULOSKELETAL RESEARCH

A Summary Report of the AAOS Research Committee Panel Studies

A document addressing:
Clinical Significance,
Current Research and Development, and
Future Research Direction
In the Care and Treatment of Musculoskeletal Health

June, 2003

AAOS Research Committee

American Academy of Orthopaedic Surgeons®

(blank page for correct printing)

This Report is a Project of the AAOS Research Committee

Marc F. Swiontkowski, MD, Chairman (2002-present)
Committee members:
Roy K. Aaron, MD
Benjamin A. Alman, MD
Gunner B.J. Andersson, MD
Robert Tracy Ballock, MD
Thomas D. Brown, PhD
Barbara D. Boyan, PhD
David A. Heck, MD
Mary I. O'Connor, MD
Sharon Stevenson, DVM, PhD
Richard M. Terek, MD

Gary E. Friedlaender, MD, Past Chairman (1999-2002)
Past Committee Members:
Wayne Akeson, MD
Benjamin Bierbaum, MD
Harold Dick, MD
William Garrett, MD
Linda Sandell, PhD

Michael Ehrlich, MD, Past Chairman (1993-1999)- Project Initiator

Caryn Prosansky, MA, Staff Liaison

To obtain additional copies of this report or additional information, please contact AAOS at

researchinfo@aaos.org

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Disclaimer

This document represents the work of seventeen distinct panels consisting of four to sixteen members each. The members of each panel are orthopaedic surgeons and/or Ph.D. level researchers who are considered experts by their peers in the given subject areas of their assigned panel. A thorough literature search was not necessarily conducted, and the literature was not reviewed with respect to levels of evidence. The recommendations and conclusions within each panel report represent the conclusions drawn by the panel Chairman, Co-Chairman, and panel members only. These reports should not be interpreted as consensus documents reflecting the opinions or policy of the AAOS Research Committee, The AAOS Council on Research and Scientific Affairs, or the AAOS membership at large. This document is intended for educational purposes and as a resource to help guide AAOS in its efforts to define directions for future musculoskeletal research.

Copyright © 2003 American Academy of Orthopaedic Surgeons. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form, or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Acknowledgments

Panel Report Editors

Marc F. Swiontkowski, MD
Thomas A. Einhorn, MD
David A. Heck, MD
James D. Heckman, MD

Panel Chairs

Panel I: Genetic, Developmental and Childhood Disorders
Michael Ehrlich, MD, chair
Steve Trippel, MD, co-chair

Panel II: Trauma and Fractures
Peter Trafton, MD, chair
Paul Tornetta III, MD, co-chair

Panel III: Hand, Upper Extremity, Microvascular Surgery and Tendons
Daniel Mass, MD, chair

Panel IV: Aging, Injury and Disability, Cartilage Structure and Function
Linda Sandell, PhD, chair
David Eyre, PhD, co-chair

Panel V: Tissue Engineering
George Muschler, MD, chair

Panel VI: Gene Therapy
Jay Lieberman, MD, chair

Panel VII: Statistics and Outcomes Research
Marc Swiontkowski, MD, chair

Panel VIII: Aging and Disability, Bone Structure and Function
Barbara Boyan, PhD, chair

Panel IX: Health Policy Research
Alan Morris, MD, chair

Panel X: Women's Health Issues
Leigh Callahan, PhD, chair
William Garrett, MD, co-chair

Panel XI: Spinal Problems
Gunnar Andersson, MD, chair
Ed Hanley, MD, co-chair

Panel XII: Neoplasia
Mary O'Connor, MD, chair
Mark Gebhardt, MD, co-chair

Panel XIII: Infections
Michael Patzakis, MD, chair

Panel XIV: Sports, Fitness and Ligaments
Wayne Akeson, MD, chair

Panel XV: Bioengineering and Biomaterials
Bernard Stulberg, MD, chair
Joshua Jacobs, MD, co-chair

Panel XVI: Joint Replacement
Roy Aaron, MD, chair
James Callaghan, MD, co-chair

Panel XVII: Workplace Injuries and Ergonomics
Sheldon Simon, MD, chair
William Marras, MD, co-chair

Staff Editors

Sylvia I. Watkins-Castillo, PhD
Caryn M. Prosansky, MA
AAOS Department of Research & Scientific Affairs

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Table of Contents

Introduction 1

MUSCULOSKELETAL RESEARCH FOCUS AREAS (in order of frequency in panel reports)

Focus Areas Identified by Seven or More Panels
- Genetic research: tissue engineering 3
- Cell biology: basic cellular research/ understanding 4
- Genetic research: biomarkers / gene therapy 5
- Biomechanics/ biophysics (kinematics & modeling) 6
- Outcomes: assessment tools, clinical trials, performance measures 7

Focus Areas Identified by Four to Six Panels
- Biomaterials: Fixation frames / injury repair 8
- Injury: epidemiology and prevention 9
- Impacts of aging 9
- Infection / Patient Safety 10
- Pain research, including drug efficacy 10

Focus Areas Identified by One to Three Panels
- Gender variance in MS conditions/ predispositions 11
- Monitoring technologies: Imaging/sensors 11
- Genetic diseases: epidemiology 12
- Musculoskeletal research awareness 12
- Osteoarthritis: epidemiology/ predisposition and risk factors 13
- Public health: disparities / patient care delivery 13
- Sports injuries: physical activity and impact 14
- Surgical technology & techniques 14
- Workforce / workplace injuries & impact 15
- Physician education / practice management 15
- Musculoskeletal Focus Research Areas Summary Table 16

AAOS Research Panel Reports
- I: Genetic, Developmental and Childhood Disorders 17
- II: Trauma and Fractures 21
- III: Upper Extremity: Microvascular, Nerve, and Tendon Research 27
- IV: Aging, Injury and Disability, Cartilage Structure and Function 31
- V: Tissue Engineering 35
- VI: Gene Therapy 41
- VII: Statistics and Outcomes Research 45
- VIII: Aging and Impairment, Bone Structure and Function 49
- IX: Health Policy Research 53
- X: Gender and Sex Issues 57
- XI: Spinal Problems 61
- XII: Neoplasia 65
- XIII: Infections 73
- XIV: Sports, Fitness, and Ligaments 77
- XV: Bioengineering and Biomaterials 85
- XVI: Joint Replacement 93
- XVII: Workplace Injuries and Ergonomics 97

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Introduction

This report is intended to raise awareness regarding important areas of musculoskeletal research and to guide the AAOS in its health policy and research advocacy activities over the next decade.

The original AAOS Research Agenda, commonly known as the Gartland Report, was created in the 1980's. In 1999, the Research Committee initiated this expanded and timely update. Seventeen areas of musculoskeletal care were identified and expert panels were created. Each panel was charged with developing a report that discussed the scope, including the clinical significance and importance to public health, recent advances in treatment or knowledge, and a list of important future research directions, for the assigned topic.

This current report targets four key audiences:

- Fellows of the Academy and the Orthopaedic Research Society, who will use this document as a statement of the topics on which orthopaedic research might best focus;
- The public, as an overview of the work being undertaken on its behalf to address musculoskeletal conditions;
- Granting agencies, such as the NIH, as a statement of important musculoskeletal areas in need of research funding; and
- Students considering careers in musculoskeletal science and scientists in training, as a statement of the directions in which orthopaedics is heading.

The research directions identified in the 17 panel reports have been sorted into 20 common themes or "Musculoskeletal Research Focus Areas". Table 1 on Page 16 shows these Focus Areas and where they are addressed in the various panel reports.

The most common research themes, included by seven or more of the panels, address four focus areas related to tissue engineering and genetic research. Also included in this top list is the collection of outcomes data on treatment effects to further knowledge and support evidence-based practices, thus serving to help reduce the major burden of disease caused by musculoskeletal conditions.

A second grouping of common themes, found in four to six panel, includes injury prevention and repair, effects of aging, patient safety, and pain research.

The final grouping of research themes, identified by one to three of the panels, addresses specific conditions, such as osteoarthritis and genetic conditions, research in gender predisposition variations, disparities in musculoskeletal treatment, sports and workplace injuries, and orthopaedic workforce training and education.

The following pages include a brief discussion for each "Musculoskeletal Research Focus Area," with key panel future research directions summarized, followed by the 17 individual panel reports.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Musculoskeletal Research Focus Areas

Focus Areas Identified by Seven or More Panels

❖ *Tissue engineering*

Tissue engineering can be defined as any effort to repair, augment, replace or regenerate a specific tissue in a specific anatomic location. Modern tissue engineering includes traditional applications of "biologically inert" materials, such as metal alloys, ceramics, and polymers. However, it expands upon conventional strategies through the development and use of 'biologically active' materials, surfaces, and bioactive compounds using a cell-based strategy. The tissues of particular interest and value to the field of orthopaedic surgery and musculoskeletal medicine are bone, cartilage, tendon, ligament, meniscus, intervertebral disc, fat, muscle, and nerve. The repair, augmentation, replacement or regeneration of these tissues is of central importance to every specialty and subspecialty in orthopaedic surgery, and also interfaces with a broad range of other specialties, including neurosurgery, plastic surgery, vascular surgery, general surgery, ENT, dentistry, and maxillofacial surgery.

Select Examples from Future Directions Sections of Panel Reports:

Panel II- B. *Biology of Fracture Healing*

1. Develop additional agents to accelerate normal healing
2. Elucidate causes for delayed union and nonunion
3. Develop biologic mediators to reinitiate fracture repair
4. Improve delivery systems for molecular compounds.
5. Further define the biophysical stimuli for fracture healing (ultrasound, electromagnetic fields, etc)

Panel III- E. *Peripheral Nerve /Brachial Plexus Injury*

1. Research on regeneration of peripheral nerves, especially the effect of growth factors targeted to motor and sensory fascicles
2. Identification of factors to speed nerve regeneration
3. Research on regeneration of spinal nerves, especially the effect of growth factors targeted to motor and sensory fascicles
4. Development of neural prostheses

Panel V- C. *Materials Science*

1. Ability to engineer scaffolds with complex, controlled architecture and targeted sets of physical and mechanical properties
2. Development of new surface modification strategies to promote cell adhesion, tissue integration and control cellular phenotype
3. Use of new micro- and nano-patterning technologies to create tissue scaffolds for control of cellular and molecular events
4. Use of recombinant technologies for control of materials design and synthesis

Panel X- A. *Arthritis*

3. Examining the biological repair processes and bioengineering approaches to tissue regeneration

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

❖ *Cell biology: basic cellular research/ understanding*

Cells arise in the body from progenitor or stem cells and become specialized for one or more distinct functions such as contraction, nerve conduction, secretion, absorption, or protection. This process of cell specialization is known as cell differentiation. Structural or morphological modifications during differentiation are accompanied by biochemical changes. For example, formation of red blood cells requires the differentiating cells to make specialized proteins for oxygen transport and to jettison the nucleus. Researchers in Cartilage Biology and Orthopaedics are using cellular, molecular, and genetic approaches to analyze cartilage development, growth, diseases and aging, as well as applying the emerging technology of mesenchymal stem cell-based tissue engineering to functional cartilage replacement.

<u>Select Examples from Future Directions Sections of Panel Reports:</u>

Panel V- B. *Cell Biology*

1. Knowledge of signaling pathways that control cellular proliferation, differentiation and survival in cells of mesenchymal origins (e.g., chondrocytes, osteoblasts/cytes, fibroblasts)
2. Basic knowledge of changes in protein/gene expression with disease states in native tissues, and following exposure to tissue scaffolds, exogenous cells, growth factors, gene therapy
3. Enhanced understanding of regulatory regions of genes relevant to musculoskeletal tissues

Panel VIII- A. *Cell biology*

1. Determine age-dependent variations in the way cells respond to load, hormones, and cytokines.
2. Identify all intracellular factors that regulate chondrocyte, osteoblast, osteocyte, and osteoclast formation and turnover.
3. Determine how injury alters the function of bone and cartilage cells.

Panel XI- D. *Treatment of Degenerative Spinal Disc Disease*

1. Development and evaluation of artificial intervertebral disc and nucleus. The prosthetic approach preserves motion. Existing European outcomes appear excessively “optimistic”. Presently, clinical trials in the U.S. are underway that should be supported.
2. Growth factors have been shown to stimulate matrix production in vitro and in animals. The introduction of growth factors or transporting genes into the nucleus that activate matrix synthesis or prevent matrix breakdown need development and evaluation.
3. The development of chondrocyte transport technologies to facilitate nuclear and annular repair..

Panel XV- G. *Cellular Mechanics*

1. Apply basic principles of the mechanics of materials to individual connective tissue cells to define the cellular response to mechanical stimuli and the cellular pathways involved in the transduction of mechanical inputs.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

❖ *Genetic research: biomarkers / gene therapy*

The sequencing of the human genome has changed the way we view disease and will enable clinicians to treat diseases in ways that were not possible in the past. The development of gene therapy has been an evolutionary process that began with the identification of the building blocks of life (DNA, RNA and transcription factors), the production of recombinant proteins, and the subsequent ability to deliver DNA to specific target cells. Advances in our understanding of the biological processes associated with developmental, degenerative, traumatic conditions, and cancer have allowed us to identify molecules that play a critical role in the signal transduction cascades that influence both normal and pathological cell processes. The availability of recombinant growth factors will clearly have an impact on the treatment of a variety of musculoskeletal problems. However, the ability to either inhibit or stimulate intracellular signaling pathways holds the potential to treat diseases associated with gene mutations (i.e. osteogenesis imperfecta), and a variety of clinical problems which are either systemic (i.e. rheumatoid arthritis, other inflammatory diseases, and osteoporosis) or located at a specific anatomic site (i.e. fracture nonunion pseudarthrosis of the spine, cartilage repair, osteolysis around total joint arthroplasties, and tendon, ligament or muscle injuries).

Biomarkers are substances that may be found in increased amounts in the blood, body fluids, or tissues, which may indicate the presence of certain diseases in the body. Examples of biomarkers include CA 125 (ovarian cancer), CA 15-3 (breast cancer), CEA (ovarian, lung, breast, pancreas, and gastrointestinal tract cancers), and PSA (prostate cancer). The identification of these biomarkers for diseases such as Osteoarthritis may have many treatment implications.

<u>Select Examples from Future Directions Sections of Panel Reports:</u>

Panel I- A. *Role of Genes in Musculoskeletal Conditions*

1. Identify and define the action of the genes that regulate skeletal formation, growth, and development
2. Elucidate the mechanisms by which these genes are regulated

Panel VI- A. *Musculoskeletal Genome*

Identify the subset of genes that encompass the musculoskeletal genome. Identify the genes that are causative or directly related to disease processes associated with the development of such conditions as rheumatoid arthritis, osteoarthritis, osteolysis, fracture healing, cartilage repair etc. (genetic counseling)

Panel X- A. *Arthritis*

1. Investigating the greater prevalence and triggers of arthritis in women
2. Exploring the biological and mechanical factors that influence the progression of arthritis
3. Examining the biological repair processes and bioengineering approaches to tissue regeneration

Panel XII- A. *Genetics in Sarcoma*

1. *Molecular Staging*

With few new chemotherapeutic agents on the horizon for the treatment of sarcoma patients, large prospective clinical studies should be performed to identify genetic markers (e.g. translocations in EFT and MDR gene in osteosarcoma) and define their prognostic significance. Other markers that may have prognostic impacts in treatment of patients with osteosarcoma, such as INK4A, Her-2-Neu and VEG-F should similarly be evaluated. Such combined investigations will require tissue procurement at the time of diagnosis and clinical correlation. If proven, these markers may allow patients at high risk for relapse to be treated with more aggressive or different therapies than patients at lower risk.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

❖ *Biomechanics/ biophysics (kinematics & modeling)*

Biophysics seeks to understand the basic mechanisms of processes in living matter, using the principles and tools of physics. Biophysicists are interested in the soft biological materials which are the building blocks of living cells and organs. There are many challenging and unanswered questions in the field of biology. In general, the complexity of the questions increases with the size of the biological materials. Investigations of the structures, energetics, thermodynamic properties, and dynamics of self-assembling biological molecules such as lipids, proteins or deoxyribonucleic acid (DNA), represent a major effort in Molecular Biophysics. Studies of the regulation mechanisms of cellular components, kinetics of ion transport, and electrical properties of cell membranes are the focus of Cellular Biophysics. Finally, the functions and signal processing within an organ (such as the brain) and the interactions of radiation with tissues belong to Tissue Biophysics.

Skeletal tissues respond to demands of their physical environment by altering the synthesis and organization of the extracellular matrix. Skeletal tissues develop and organize themselves according to mechanical strain patterns. Orthopaedists recognize this in the clinical conditions of atrophy and hypertrophy. The clinical specialty of Orthopaedics is built largely on the therapeutic manipulation of the physical environment of skeletal tissues to allow and potentially stimulate repair. Current research is being directed at how repairing skeletal tissues respond to physical cues and what translational opportunities exist. Active investigations are underway to understand the therapeutic potential of mechanical strain, electrical fields, and ultrasound in stimulating skeletal repair.

<u>Select Examples from Future Directions Sections of Panel Reports:</u>

Panel V- E. *Biomechanics - Biophysics*

1. Establish biomechanical and biophysical parameters of requirements for successful tissue-engineered replacements
2. Develop tissue scaffolds to recreate the biomechanics and biophysics of native tissue
3. Advance knowledge of the mechanical and physical signals relevant to cells within healthy tissues and material replacements
4. Advance the use of physical signals in bioreactor design to modify tissue growth ex vivo
5. Bioreactor technology controlling and simulating biological conditions of mass transport

Panel XI- I. *Biomechanics*

1. Biomechanics of Spinal Degeneration: Human disc, ligaments, and the facets work in unison to transmit loads and motions across a motion segment or functional spinal unit (FSU). The FSU consists of two adjacent vertebrae and the interconnecting ligaments and disc. For this reason, if the degenerative process affects one component others follow. In general, degenerative changes result in decreased disc heights, increased ligament laxity, and decreased ROM. Recent efforts are underway to restore disc function by replacing the disc with a “mechanical” disc and restoring the collapsed osteoporotic vertebral bodies with cement. It is important that the interaction between biomechanics and biology be pursued at the cellular level to gain further understanding of the role of mechanical factors in producing degeneration, in preventing/slowing down the degeneration, and/or replacing a degenerated spinal element. 2. Biomechanics of Motion Segment and Clinical Instability: FSU mechanical properties vary with spinal level and motion direction, mostly because of the varying vertebral size, facet orientation, and disc geometry. Modern imaging techniques, such as MRI, may enable us to study the in situ response of FSU in patients with various spinal disorders, including spinal instability. New technological advances in the area of micro- and nano-scare sensors may afford a unique pathway to determine in situ loads in subjects during activities of daily living.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

❖ *Outcomes: assessment tools, clinical trials, performance measures*

Outcomes research requires the collection of patient-oriented information. Questionnaires have been developed to determine patients' assessments of their physical and mental health, quality of life, and satisfaction with care. These questionnaires, in some cases, have been incorporated into large randomized clinical trials to maximize validity and clinical utility of the investigation.

A questionnaire of health status needs to be: 1) validated, that is, measure what it is supposed to, 2) reproducible, that is, result in the same answer each time it is administered in the absence of a change in health status, and 3) responsive, that is, sensitive to clinically important changes. There are generic health measures that measure general function and quality of life. In addition, there are disease specific questionnaires that focus on a particular disease entity. The SF-36 is a well-validated measure of general health, but disease-specific measures may show greater change in the treatment of orthopaedic conditions.

A performance measure is defined as a quantitative assessment of health care processes and outcomes for which an individual physician or other practitioner, provider organization or health plan may be accountable. That is, it assesses the physician's treatment course in order to determine what course will result in the best possible outcome for the patient.

<u>Select Examples from Future Directions Sections of Panel Reports:</u>

Panel II- G. *Outcomes and Economic Issues*:

1. Further elucidate outcomes of specific injuries for
    a. patient-based outcomes
    b. societal cost of injury
    c. investigate the impact of rehabilitation strategies
2. Cost effectiveness of management options to:
    a. optimize management to improve
    b. assess time out of work
    c. assess ability to return to same job
    d. identify job modification techniques
    e. evaluate occupational therapeutics

Panel VII- H. *Address Barriers to Developing Successful Outcomes Systems*

The technological barriers are being overcome, especially with new Web-based technology. The psychological barriers, including physician reluctance to share data, and the difficulty of demonstrating added value for participating physicians remains. Additional barriers to data collection may arise in conjunction with new federal regulations regarding data confidentiality, a consequence of the 1996 Health Insurance Portability and Accountability Act, otherwise known as HIPAA.

I. *Reduce Burden of Outcomes Data Collection*

Attempt to reduce physician burden of data collection and at the same time recognize that there are multiple end users of patient-based data. These end users include: physicians in quality improvement initiatives, accrediting bodies for credentialing, boards for maintenance of certification, and payers for accountability and choice. It must be recognized that the identical outcomes data can be used by the various end users for quite disparate purposes.

J. *Utilize Outcome Data to Educate Patients*

Encourage and further study the utilization of outcome data in educating patients to enhance their participation in decision making about treatment choices.

K. *Research Patient Characteristics that Impact on Outcomes*

Develop a greater understanding of which patient characteristics are associated with better and worse outcomes and how these risk factors may be mitigated.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

Focus Areas Identified by Four to Six Panels

❖ *Biomaterials: Fixation frames / Joint Replacement / Injury repair*

Constant biomechanical and structural improvements of external fixation frames has resulted in a gradual increase in their use by orthopaedic and traumatology surgeons. However, complications can result, especially infection. New methods and materials, both for designing the frames and treating the infections, need to be developed.

The development of new techniques, as well as new materials for reconstructive surgery, has had a definite impact on orthopaedics, and will continue to do so. Orthopaedic bioengineering and biomaterials research has continued to refine our understanding of how natural tissues function in normal activities of living, and how new structures and materials can be designed, manufactured, and implanted to replace those functions when disease, injury, or other forces lead to compromise in these functions.

Joints are replaced quite frequently, and new and better materials both for the joint and interface materials need to be developed. The vast majority of joint replacements are successful, and result in substantial functional improvements for the patients. This in turn permits patients to maintain independent, productive lives and reduces dependency upon institutions, family, and social services.

Transplantation can take place in as small a part of the body as the finger to as large a part as an entire hip. Transplantation of bone is a well established technology. However, transplantation of articular cartilage, ligaments and fibro-cartilagenous materials are more problematic.

<u>Select Examples from Future Directions Sections of Panel Reports:</u>

Panel XV- A. *Materials*

1. Wear
    a. Understand and reduce the interaction of prosthetic material with host
    b. Develop and refine early detection methodologies
    c. Develop models of early intervention to minimize sequella of wear
2. Prevention of Implant Failure
    a. Prosthetic design improvements
    b. Medical therapies to reduce failures
    c. Laboratory assessments of prosthetic by-products
    d. Metallic Ion effects on tissues and patients
    e. Approaches to minimize the production of debris particles
    f. Identify molecular markers of loosening/osteolysis

Panel XVI- C. *Implant Needs*

1. Develop and better understand the use of bone graft substitutes to manage osseous defects
2. *Fixation to Bone*
    a. Prosthetic surfaces and coatings
    b. Growth factors

D. *Aseptic Loosening and Osteolysis*

1. Reduce the formation of polyethylene wear and other debris
2. Better understand and reduce the biological response to particulate debris, especially with polyethylene

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

❖ *Injury: epidemiology and prevention*

Preventing and treating injury comprises a significant portion of the duties of an Orthopaedic surgeon. Research into cutting edge technology for treating fractures, as well as soft-tissue injuries, is vital to the sustenance of the field. Development of better safety equipment, as well as research into types of exercise, to help to prevent injuries, is of critical importance to the aging, but active population.

Select Examples from Future Directions Sections of Panel Reports:

Panel II- A. *Injury Prevention*

1. Falls in elderly patients
2. Effects of osteoporosis / fracture incidence reduction
3. Passenger safety in motor vehicle collisions

Panel XIV- C. *Pathomechanics of Joint Injury*

1. Development of better understanding of the pathomechanics of joint injury.
2. Development of more effective protective devices for particular sports where risks of physical impairment exist

❖ *Impacts of aging*

As the population ages, increased demand for services will be placed on the orthopaedic community. An increase in fractures related to osteoporosis and loss of bone mineral appears to be a major issue at this time. The early diagnosis and effective implementation of treatments to reduce the risk of fracture is important.

Other diseases, such as osteoarthritis, will have a dramatic impact on the health of the elderly. It is estimated that over 50% of all persons aged sixty or above will suffer from cartilage degeneration. Treatments for this disorder include medical management, rehabilitative interventions, and total joint replacement. Other surgical interventions such as arthroscopic intervention and cartilage implantation need to be better evaluated and understood.

Muscle loss associated with aging is recognized. Fitness programs will need to be specially designed for the elderly to help avoid injury. As the population continues to live longer, and the average age of the US work force increases, the impact of aging on work-related loading, tolerance, psychosocial stress, and their interactions needs to be better understood.

Select Examples from Future Directions Sections of Panel Reports:

Panel XVIII- A. *Cell biology*

1. Determine the age-dependent variations in the ways cells respond to load, hormones, and cytokines
2. Identify the intracellular factors that regulate chondrocyte, osteoblast, osteocyte, and osteoclast formation and turnover
3. Determine how bone and cartilage injury alters the function of their respective cells

Panel XVII- D. *Magnitude and Impact of Shoulder Injuries*

Worldwide trends have shown that shoulder problems are common and are occurring with increased frequency in the workplace. This trend appears to be unrecognized in US industry. Better surveillance is needed to appreciate the magnitude of risk associated with shoulder loading in the workplace. As people live longer, and the average age of the US work force increases, the impact of aging on work-related loading, tolerance, psychosocial stress, and their interactions must be better investigated.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

❖ *Infection / Patient Safety*

Orthopaedic surgery involves many invasive procedures. There is great risk of infection whenever surgical intervention is performed. Methods for treating and preventing these infections are a major focus within orthopaedic research. Elderly people are more susceptible to infection, and are also the most likely candidates of joint replacement. Thus, attention devoted to infection is extremely important.

A report released by the Institute of Medicine in 1999 "To Err is Human..." and several Congressional hearings have focused public attention on the need to improve patient safety and minimize medical errors. Historically, medical errors in orthopaedics (e.g., wrong site surgery) have been of great concern to the Orthopaedic community, and programs have been and continue to be implemented to prevent such errors and improve patient safety.

<u>Select Examples from Future Directions Sections of Panel Reports:</u>

Panel II- E. *Complications of Fractures*

1. Improve treatment of skeletal infection with local measures and systemic adjuncts
   a. Further determine the relationship between deformity and outcomes
   b. Develop and evaluate the effectiveness of bone graft substitute

Panel XIII- H. Determine methods that will lead to early and accurate detection of infection.

I. Investigate the cause(s) of and develop preventative strategies to reduce the potential for implant infection

J. Develop and explore the use of biodegradable antibiotic delivery systems.

K. Study bacterial mechanisms of producing disease to determine new ways to attack or eliminate bacterial infections

❖ *Pain research, including drug efficacy*

Pain is an unfortunate side effect of many musculoskeletal conditions. As cartilage wears away and bones rub against each other, joint pain results. Surgical interventions often result in pain as part of the recovery process. Research into both drug efficacy for reducing and controlling pain, as well as biological / neurological components of pain (such as factors that mediate pain perception) is an important area for further investigation.

<u>Select Examples from Future Directions Sections of Panel Reports:</u>

Panel III- B. *Microvascular*

1. Identify the links, if any, between factors that regulate microcirculation and those which mediate pain perception

Panel XI- F. *Treatment of Chronic Back and Neck Pain*

Chronic pain, not only as it applies to the painful spine but to all musculoskeletal areas, requires a different approach than acute pain. Current treatment alternatives range from medication to implantable stimulators and behavioral modification. All of these treatment alternatives require further study and none has been found to be singularly effective in large groups of patients.

J. *Neurobiology / Pain Research*

In acute and subacute pain, the nociceptors are sensitized by chemicals released from the immune system, vascular system, nerve endings, and injured tissue. These chemicals include bradykinins, prostaglandins, histamine, substance P, and cytokines. These chemicals either sensitize or activate nociceptors. Cytokine inhibitors and membrane channel blockers that act on specific sites in the peripheral and central nervous system may be useful in alleviating musculoskeletal pain in the future.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Focus Areas Identified by One to Three Panels

❖ *Gender variance in MS conditions/ predispositions*

Women are affected by various orthopaedic conditions at different rates than are men. For example, osteoarthritis is 3 to 4 times more common in women than in men. Eighty percent (80%) of patients affected by osteoporosis are women. Studies have revealed increased rates of musculoskeletal injuries among females participating in athletics. With the recognition of not only differences in disease prevalence and type between men and women, but of differences at the cellular and biological levels as well, investigating these differences in musculoskeletal system growth, repair, and interactions with other systems are necessary.

Select Examples from Future Directions Sections of Panel Reports:

Panel X- B. *Arthritis*

1. Investigate why there is a greater prevalence of arthritis in women than in men.
2. Explore the biological and mechanical factors that trigger the development and progression of arthritis.
3. Investigate how the biological repair processes and bioengineering approaches to tissue regeneration, replacement, and repair in men and women might be different.
4. Develop sex-specific markers for osteoarthritis and rheumatoid arthritis.
5. Develop sex-specific animal models for the study of the molecular mechanisms of osteoarthritis and rheumatoid arthritis.

C. *Osteoporosis*

1. Explore the sex-specific factors that contribute to the development of peak bone mass.
2. Develop additional biologic markers for early detection of bone loss.
3. Develop genetic markers for detecting persons at risk for bone loss.
4. Develop and enhance imaging technologies that enable the early detection of bone loss.
5. Develop strategies which will optimize the maintenance of bone mass throughout life.
6. Develop strategies for improving the quality of life in women with osteoporotic fractures.
7. Explore the role of physical activity in preserving muscle strength, balance, and coordination as a means of enhancing bone quality and preventing falls in the elderly.
8. Develop agents that will stimulate bone formation and maintain bone quality.

❖ *Monitoring technologies: Imaging/sensors*

Different methods of imaging and sensing help in both diagnosing and treating Orthopaedic conditions. As technology continues to evolve, new methods will be created. Translating this new technology into practical applications for Orthopaedic surgeons will be a leading field of study in the years to come.

Select Examples from Future Directions Sections of Panel Reports:

Panel XV- D. *Imaging Technologies*

1. Radiographic evaluation of fixation- Radio Stereometric Analysis (RSA)
2. Radiographic evaluation of remodeling- Dual-Energy X-Ray Absorptiometry (DEXA)
3. Radiographic evaluation of wear
4. Improved implantation technologies- Image Guided Surgery (Surgical Navigation)
5. Robotic surgical techniques
6. Tele-surgery
7. Instrumentation for minimally invasive surgery

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

❖ *Genetic diseases: epidemiology*

Genetic, developmental and childhood disorders of the musculoskeletal system are a lifelong burden. Not only do they affect the quality of life of the children who suffer the consequences of their disease, but they often lead to continued or progressive problems into adolescence, adulthood, and even into subsequent generations. Disturbances of joint formation during growth can lead to early development of arthritis. Localized malformations of the musculoskeletal system range in severity from mild toe or finger abnormalities to the absence of limbs. Defects in skeletal growth cause a variety of types of dwarfism, short stature, and other skeletal deformities. Failure of the development of the axial skeleton can produce bone, muscle, and nerve abnormalities that range in severity from insignificant to lethal. The economic impact of genetic, developmental and childhood disorders is difficult to determine because of the wide variety of conditions and the limited available data. The total cost of musculoskeletal deformities was estimated at $862 million in 1995, excluding morbidity costs. The total costs reported, however, were felt to be clearly underestimated. The emotional, personal, social, and other non-monetary costs of childhood disorders are incalculable, particularly when extrapolated through the lifetime of the individual.

Select Examples from Future Directions Sections of Panel Reports:

Panel I- A. *Role of Genes in Musculoskeletal Conditions*

1. Identify and define the action of the genes that regulate skeletal formation, growth, and development.
2. Elucidate the mechanisms by which these genes are regulated.

❖ *Musculoskeletal research awareness*

Because musculoskeletal conditions usually affect quality of life, and are usually only indirectly life-threatening, they do not always receive the same attention as other health conditions which possess a more immediate threat to life. However, quality is an important part of life, and thus, it is imperative that we increase awareness of policy-makers to musculoskeletal conditions in order to continue to fund research in these areas.

Select Examples from Future Directions Sections of Panel Reports:

Panel VII- C. *Utilize the Burden of Disease*

Documentation of musculoskeletal burden of disease data being developed for the Bone and Joint Decade should be the single most important research effort for AAOS, and should be used to help set priorities based upon the impact to the population.

❖ *Osteoarthritis: epidemiology / predisposition and risk factors*

Osteoarthritis affects multiple joints in the human body, and as a person ages, the risk of developing osteoarthritis increases. It is caused by the wearing away or injury of the cartilage at the joint, resulting in pain when bone rubs on bone. Understanding the progression of the disease, the predisposing and risk factors for development, and development of new methods for growing cartilage, as well as new materials and techniques for both treatment and artificial joints is of substantial importance within the field of Orthopaedic research.

Select Examples from Future Directions Sections of Panel Reports:

Panel IV - C. *Osteoarthritis*

Metabolic changes in cartilage preceding and accompanying osteoarthritis

a. Degradative enzymes
b. Apoptosis
c. Proliferation and anabolic events

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

❖ *Public health: disparities / patient care delivery*

Health disparities are defined as a relatively greater or lesser need, willingness, or unmet need of specific population sub-groups, as related to access of care, based on sex, race, ethnicity, or socioeconomic status. Studies have shown that disparities do exist. More research must be conducted in order to determine which groups are being over- or under-served, and to create ways to remedy this situation.

Select Examples from Future Directions Sections of Panel Reports:

Panel IX- D. *Delivery of Orthopedic Care*

1. Develop outcomes data to assess the impact on quality of life and cost-effective treatments.
2. Identify the methods of obtaining outcomes data in the clinical office setting addressing the time, workforce, and cost involved in gathering this data.
3. What are the barriers to domestic volunteerism among orthopaedic surgeons and how can they be removed? Is orthopaedic volunteerism effective in improving the delivery of musculoskeletal care to underserved areas in the U.S.?

❖ *Sports injuries: physical activity and impact*

As has been mentioned in several other sections, physical activity is directly related to orthopaedic science. Active sporting participants are likely at some point in their exertion to become injured. These injuries are likely contributors to later-developing osteoarthritis. Physical activity impacts both genders differently. Age is also a consideration; in the future, programs need to be designed for age-specific groups in order to insure safety. Physical activity has been shown to help increase bone density, thus decreasing the risk of osteoporosis. Physical activity helps reduce obesity, which contributes to strain on the joints.

Select Examples from Future Directions Sections of Panel Reports:

Panel XIV-B. *Impact of Inactivity*

Development of better understanding of the impact of inactivity with respect to common pathologic mechanisms in cardiovascular, musculoskeletal, and neurological diseases or disorders.

F. *Exercise Impact on Osteoporosis*

Development of concepts leading to guidance to the general population in all age groups for reducing the risk of osteoporosis by optimizing weight-bearing exercise protocols and resistance-training protocols.

❖ *Surgical technology & techniques*

Orthopaedic techniques are continuously changing as newer technologies emerge. An effort must be made to train surgeons in these new technologies in order for them to keep current with cutting edge treatments.

Select Examples from Future Directions Sections of Panel Reports:

Panel XI- E. *Emerging Technologies*

Emerging technologies in spine care include intradiscal treatment using heat-generating devices. These treatments aim primarily at the painful degenerative disc. The basic science underlining the procedures remains unclear. Other emergent technology includes vertebroplasty and kyphoplasty. In both of these procedures, vertebral fractures are treated by injection of bone cement. In kyphoplasty, a balloon is first inserted, aimed at obtaining deduction and providing a cavity for the cement. Replacement of the nucleus pulposus, so- called nucleoplasty of the entire disc, and so-called disc replacement, are other emerging technologies. These procedures also

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

address the painful intervertebral disc. While early results are encouraging, all these emerging technologies should be further tested in randomized controlled trials, and their long-term results remain uncertain at the present time.

❖ *Workplace injuries & impact*

Musculoskeletal injuries related to the workplace are among the most costly health problems facing society today. In 1999, almost 1 million people took time away from work to be treated and to recover from work-related musculoskeletal pain or impairment of function. The importance of ergonomics to orthopaedic surgery lies in its potential to prevent primary musculoskeletal disorders attributable to work, as well as in its potential to minimize the risk of re-injury or secondary injury when returning to the workplace. The goal of ergonomic science is to understand the causality of work-related musculoskeletal disorders and use this knowledge to reduce work-related risk. Traditionally, the disciplines of biomechanics, physiology, and psychophysics have dominated the body of knowledge that has defined exposure limitations to work.

Select Examples from Future Directions Sections of Panel Reports:

Panel XVII- G. *Continued Understanding of Causality and Role of Intervention in Workplace Injuries*
A continuing need exists for high-quality intervention studies. Most research has focused on the causal relationship between work and musculoskeletal disorders. However, the effectiveness of intervening in this relationship can be established only through high quality intervention studies. Studies must overcome the traditional limitations in these efforts to better establish causality and effectiveness of interventions.

❖ *Physician education / practice management*

Medical education, in general, must adapt to new and emerging technologies. Educating new physicians in the most cutting-edge methods and surgical techniques is a challenge that must be met. Evaluating competency with these techniques must also be emphasized. Increasing diversity in the Orthopaedic work force is imperative, and must begin at the medical education level, and continue through to hiring practices.

Select Examples from Future Directions Sections of Panel Reports:
Panel IX- B. *Work Force*

1. Maintain an accurate data base and continually update the institution's knowledge and expertise related to the musculoskeletal physician workforce (survey research to include in particular the short- and long-term effects on the scope of practice of the younger members).
2. How to address and improve diversity in orthopaedic training and manpower?
3. Projections of future need?

F. *Physician Education*

1. Refine the educational effectiveness of motor skills testing and virtual reality operating experiences as a measure of competence.
2. Does current residency curriculum and testing (driven by the AAOS Orthopaedic Knowledge Update) translate into competence?
3. Can changes be made in the medical school and resident training curriculum for MD/DO providers of musculoskeletal care (i.e. introducing data on managing malpractice risk) and how would such changes alter the delivery of care?

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Table 1 Musculoskeletal Research Focus Areas Identified by Research Committee Panels

Table 1	Musculoskeletal Research Focus Areas Identified by Research Committee Panels																	
	Panel Point Identified as Musculoskeletal Research Focus Area																	
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	
Research Focus Area	Genetic, Developmental and Childhood Disorders	Trauma and Fractures	Upper Extremity, Microvascular, Nerve and Tendon Research	Aging, Injury and Disability, Cartilage Structure and Function	Tissue Engineering	Gene Therapy	Statistics and Outcomes Research *	Aging and Impairment, Bone Structure and Function	Health Policy Research*	Gender and Sex Issues	Spinal Problems	Neoplasia	Infections	Sports, Fitness, Muscles and Ligaments	Bioengineering and Biomaterials	Joint Replacement	Workplace Injuries and Ergonomics	Total Panels Indentifying as Research Focus
Tissue engineering	C	B/E	B-E	A	C/D	F		B/G		A/B3	D/H	B/C	G					11
Cell biology: basic cellular research/ understanding				C	A/B			A/C/ D/F			D/H	A/C/D	A/K	H/I	G		C	9
Biomarkers / gene therapy	A/B			B		A-D		I		B/C	D/H	A	F					8
Biomechanics/ biophysics (kinematics & modeling)				E	E			J/K			I			J	C/E	B/E		7
Outcomes: assessment tools, clinical trials, performance measures	D	G					A/B/H/ I-N		D		B				F	G/H		7
Biomaterials: fixation frames / injury repair				D				B2/E				B1		G	A/B	A/C/D		6
Injury: epidemiology and prevention		A/C/ D/F		B1				A/D1/ E2		D				C			B/D/E	6
Impacts of aging; care of elderly		D		H				A/H						A			D	5
Infection / Patient Safety		C/E				G			E				B-E/ H-K			F		5
Pain research, including drug efficacy			B2								F/J	C					C	4
Gender variance in MS conditions/ predispositions				G						B/C/D/E				A/E				3
Monitoring technologies: Imaging/sensors					F/G							D2			D			3
Genetic diseases: epidemiology	A										G							2
Musculoskeletal research awareness							C-G		A									2
Osteoarthritis: epidemiology				B2/C1/ D2b/F						B								2
Public health: disparities / patient care delivery									C/G/H					K/L				2
Sports injuries: physical activity and impact										C/D				A/B/D/F				2
Surgical technology & techniques			A								A/C/E							2
Workplace injuries & impact																	A/F/G	1
Physician workforce: education & practice management									B/F									1
Table Key: A, B, C2, etc — Denotes the specific location of the point in the Future Directions section of individual panel reports where the focus area is presented.																		

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel Reports

Panel I: Genetic, Developmental, and Childhood Disorders

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Genetic, developmental and childhood disorders of the musculoskeletal system are a lifelong burden. Not only do they affect the quality of life of the children who suffer the consequences of their disease, but they often lead to continued or progressive problems into adolescence, adulthood, and even into subsequent generations. Disturbances of joint formation during growth can lead to early development of arthritis. Localized malformations of the musculoskeletal system range in severity from mild toe or finger abnormalities to the absence of limbs. Defects in skeletal growth cause a variety of types of dwarfism, short stature, and other skeletal deformities. Failure of the development of the axial skeleton can produce bone, muscle, and nerve abnormalities that range in severity from insignificant to lethal.

B. *Importance to Public Health*
The economic impact of genetic, developmental and childhood disorders is difficult to determine because of the wide variety of conditions and the limited available data. The total cost of musculoskeletal deformities was estimated at $862 million in 1995, excluding morbidity costs. The total costs reported, however, were felt to be clearly underestimated.. The emotional, personal, social, and other non-monetary costs of childhood disorders are incalculable, particularly when extrapolated through the lifetime of the individual.

II. RECENT ADVANCES

A. Relationship between the molecular/genetic defect and clinical manifestations of the disease.
   1. Osteogenesis imperfecta: The specific molecular defect in the formation of Collagen I predicts the severity of the disease.
   2. Achondroplasia defective fibroblast growth factor receptor 3 explains the abnormal cartilage growth in the physics of long bones, the posterior elements of the spine, and the chondrocranium.

B. Advanced structural studies including immunocytochemistry, histochemistry, confocal microscopy, three-dimensional reconstruction, and ultra-structural assessments have explained the relationship between skeletal dysplasia in childhood and osteoarthritis in adults.

C. Understanding the signaling pathways through PTHrP or IHH is leading to an understanding of how collagen grows and matures and its effect on fracture healing and growth.

D. Development of modern spinal instrumentation with its subsequent reduction in cost and suffering. Patients used to be kept supine in body casts for six months and would spend often months in the hospital in traction. Now they are home, walking around, within a week.

E. Development of specialized external fixation frames and research into bone regeneration. Correction of angular deformities and new techniques of leg lengthening have led to limb salvage for previously hopeless cases.

F. Developing patient-based outcome assessment tools for disorders in children and using them in clinical outcomes studies.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

III. FUTURE DIRECTION OF RESEARCH

A. *Role of Genes in Musculoskeletal Conditions*
   1. Identify and define the action of the genes that regulate skeletal formation, growth, and development.

   2. Elucidate the mechanisms by which these genes are regulated.

B. *Cell-Regulatory Research*
   Discover the actions and interactions of cell-regulatory proteins and their target cells in normal and abnormal conditions.

C. *Physiologic Interventions*
   Develop more physiologic interventions for the correction of skeletal deformities.

D. *Outcomes Studies of Therapeutic Approaches*
   Design and conduct clinical trials to determine optimal therapeutic approaches to these conditions as new treatments are developed.

IV. REFERENCES

Bell DF, Boyer MI, Armstrong PF: The use of the Ilizarov technique in the correction of limb deformities associated with skeletal dysplasia. *J Pediatr Orthop* 1992: May-Jun;12(3):283-290.

Blakemore LC, Scoles PV, Poe-Kochert C, Thompson GH: Submuscular Isola rod with or without limited apical fusion in the management of severe spinal deformities in young children: Preliminary report. *Spine* 2001; Sep 15;26(18):2044-2048.

Bleasel JF, Holderbaum D, Mallock V, et. al.: Hereditary osteoarthritis with mild spondyloepiphyseal dysplasia—Are there “hot spots” on COL2A1? *J Rheumatol* 1996; Sep;23(9):1594-1598.

Farquharson C, Jefferies D, Seawright E, Houston B: Regulation of chondrocyte terminal differentiation in the postembryonic growth plate: The role of the PTHrP-Indian hedgehog axis. *Endocrinology* 2001; Sep;142(9):4131-4140.

Gordon JE, Jani M, Dobbs M, et.al.: Treatment of rigid hypertrophic posttraumatic pseudarthrosis of the tibia in children using distraction osteogenesis. *J Pediatr Orthop* 2002; Jul-Aug;22(4):419-423.

Horton WA: Review: Fibroblast growth factor receptor 3 and the human chondrodysplasias. *Curr Opin Pediatr* 1997; Aug;9(4):437-442.

Juppner H: Review: Role of parathyroid hormone-related peptide and Indian hedgehog in skeletal development. *Pediatr Nephrol* 2000;Jul;14(7):606-611.

Katzenstein PL, Malemud CJ, Pathria MN, et. al.: Early-onset primary osteoarthritis and mild chondrodysplasia. Radiographic and pathologic studies with an analysis of cartilage proteoglycans. *Arthritis Rheum* 1990; May;33(5):674-684.

Kuklo TR, Lenke LG, Won DS, et.al.: Spontaneous proximal thoracic curve correction after isolated fusion of the main thoracic curve I [MISSING SOMETHING?] adolescent idiopathic scoliosis. *Spine* 2001; Sep 15;26(18):1966-1975.

Millet PJ, Lane JM, Paletta GA Jr: Limb salvage using distraction osteogenesis. *Am J Orthop* 2000; Aug;29(8):628-632.

Praemer A, Furner S, Rice DF (eds): *Musculoskeletal Conditions in the United States*. Rosemont, IL, American Academy of Orthopaedic Surgeons, 1999.

Raimondo RA, Skaggs DL, Rosenwasser MP, Dick HM: Lengthening of pediatric forearm deformities using the Ilizarov technique: Functional and cosmetic results. *J Hand Surg Am* 1999; Mar;24(2):331-338.

Sztrolovics R, Glorieux FH, Travers R, van der Rest M, Roughley PJ: Osteogenesis imperfecta: Comparison of molecular defects with bone histological changes. *Bone* 1994, May-June;15(3):321-328.

Vajo Z, Francomano CA, Wilkin DJ: Review: The molecular and genetic basis of fibroblast growth factor receptor 3 disorders: The achondroplasia family of skeletal dysplasias, Muenke craniosynostosis, and Crouzon syndrome with acanthosis nigrans. *Endocr Rev* 2000; Feb;21(1):23-39.

Wenstrup RJ, Willing MC, Starman BJ, Byers PH: Distinct biochemical phenotypes predict clinical severity in nonlethal variants of osteogenesis imperfecta. *Am J Hum Genet* 1990; May;46(5):975-982.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Wright JG: The fallacy of short-term outcome analysis in pediatric orthopaedics. *J Bone Joint Surg Am* 2001; Apr;83-A(4):620-621.

Young NL, Wright JG: Review: Measuring pediatric physical function. *J Pediatr Orthop* 1995; Mar-Apr;15(2):244-253.

V. PANEL MEMBERS

Chair:	Michael Ehrlich, MD	Brown University	Providence, RI
Co-chair:	Stephen Trippel, MD	Indiana University Medical Center	Indianapolis, IN
	James Aronson, MD	University of Arkansas for Medical Sciences	Little Rock, AR
	Regis O'Keefe, MD	University of Rochester Medical Center	Rochester, NY
	Fred Shapiro, MD	Children's Hospital Medical Center	Boston, MA
	Stuart Weinstein, MD	University of Iowa Hospital	Iowa City, IA

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel II: Trauma and Fractures

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Research in these areas is directed toward improving the outcomes of patients with fractures, those with posttraumatic sequelae or complications from musculoskeletal injury, and toward prevention of injury. Musculoskeletal injury can be isolated, such as an ankle fracture, or part of a more complex constellation of injuries, such as a patient with multiple fractures and organ damage from a motor vehicle crash.

B. *Importance to Public Health*
Accidents are the largest cause of death and disability in the young adult age group. More than 70% of nonfatal accident victims who are multiply injured sustain a skeletal injury requiring treatment. In addition to the health care costs, these injuries cause billions in the opportunity costs of lost employment and can cause lifetime disability.

At the other end of the age spectrum, normal bone loss in the elderly predisposes them to fracture. It is estimated that 50% of women over age 50 years and 33% of men over age 70 years will sustain a fracture secondary to osteoporosis. Hip, wrist, and spine fractures are most common. As the population ages, these injuries will become more prevalent. The current incidence of hip fractures is 4.5 / 100 people over the age of 70, accounting for 340,000 / year in the US alone. These fractures generate costs of approximately 8 billion dollars. This number will rise to 512,000 by the year 2040 with a projected cost of 16 billion dollars.

The prevention and treatment of fractures and multiply injured patients is the highest priority in musculoskeletal care as it affects the general public. After injury prevention, methods to reduce complications, disability, and mortality are paramount. Further refinement of operative techniques and rehabilitation will improve outcomes, facilitate return to work, and provide for a more full life of the injured patient.

II. RECENT ADVANCES

A. *Epidemiology*
The epidemiology of specific fractures within regions, age groups, and other population variables have been determined by use of regional and national databases.

B. *Biology of fracture healing*
The molecular proteins and signaling pathways of fracture healing are being elucidated. Bone morphogenic proteins have been identified and genetically engineered. The first clinical use of these proteins has demonstrated effectiveness in accelerating fracture healing. Genetic delivery systems are now being devised that will improve local placement of these substrates.

C. *Fractures in the elderly*
The special challenges of the elderly trauma patient are being investigated. has a higher risk of fracture and mortality given the same mechanism and energy of injury than a younger patient. Methods of managing elderly hip fracture patients have lowered mortality and improved outcomes over past methods. Medical management of osteoporosis has diminished the fracture rate as compared with matched patients who are untreated.

D. *Nonunion*
Identification of smoking as a risk factor has led to the recommendation to cease smoking after fracture. Improved surgical techniques including microvascular free tissue transfer, bone

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

transport, and bone graft supplements have allowed for the reconstruction of fractures with significant bone defects and infection.

E. *Mangled extremities*
A large multi-center observational study has evaluated the initial and two-year success of limb salvage and amputation in treating the most severely injured limbs. The indicators for amputation have been more clearly delineated. Patient factors such as education, income, and personality profiles have a major effect on outcome regardless of treatment method. An increased awareness of the problems patients have after their initial treatment will focus further research into work and activity re-entry.

F. *Multi-system injury*
The systemic effects of fracture fixation in the face of other organ system injury has been examined. In particular, the fixation of long bones in the face of severe chest and head injury has been modified in many circumstances to include damage control techniques early and definitive fracture care on a slightly delayed basis. New strategies such as mechanical compression, specialized noninvasive screening, and chemical prophylaxis have decreased the rate of pulmonary emboli in trauma patients. Molecular mechanisms of systemic inflammatory reaction have been identified in further focusing research efforts to diminish sequelae such as adult respiratory distress syndrome (ARDS) and multi-system organ failure (MOF).

G. *Fracture stabilization*
New implants allow for stabilization of fractures with percutaneous techniques that reduce blood loss, decrease infection rates, and speed recovery.

H. *Emergency care*
The value of trauma systems in reducing mortality has been established. The superior management of trauma victims by designated trauma centers, likewise, has been clearly shown.

I. *Adjunctive care*
The use of ultrasound and electromagnetic fields have demonstrated decreased healing times. Specific rehabilitation protocols and team approaches to specific problems accelerate return to function.

J. *Outcome measures*
Instruments to measure patient based outcome after musculoskeletal injury have been developed and validated. These measures have demonstrated significant long term effects of skeletal trauma in the areas of physical function and psychosocial roles. They will be instrumental in the evaluation of future technologies and surgical procedures.

III. Future Directions of Research

A. *Injury Prevention*

4. Falls in elderly patients
5. Effects of osteoporosis / fracture incidence reduction
6. Passenger safety in motor vehicle collisions

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

B. *Biology of Fracture Healing*
   1. Develop additional agents to accelerate normal healing
   2. Elucidate causes for delayed union and nonunion
   3. Develop biologic mediators to reinitiate fracture repair
   4. Improve delivery systems for molecular compounds.
   5. Further define the biophysical stimuli for fracture healing (ultrasound, electromagnetic fields, etc)

C. *Systemic Injury*
   1. Continue to improve trauma systems triage and delivery
   2. Systemic effects of skeletal trauma
      a. Further elucidate inflammatory response
      b. Manipulation of cytokines and pro-inflammatory regulators
      c. Investigate effects of comorbidities on fracture care
   3. Elderly trauma patients
      a. Improve injury prevention strategies
      b. Improve medical and surgical interventions to minimize the physiologic cardiovascular stress of injury.
   4. Combined injury recognition and treatment
      a. Timing and type of surgery in multiply injured patients
      b. Head injury
      c. Chest injury
      d. Shock
   5. Deep vein thrombosis and pulmonary embolism
      a. Improve diagnosis
      b. Standardize indications and methods of prophylaxis

D. *Injury Care*
   1. Elucidate the indications for nonoperative fracture care
   2. Improve management of specific skeletal injuries
      a. Minimally invasive surgery
      b. Surgical risk reduction
      c. Continue to improve implants used for fracture stabilization
      d. Multi-center organization for comparison studies
   3. Management of the mangled extremity
      a. Multidisciplinary approaches
      b. Improving outcomes
      c. Reintegration with patient into society, retraining
   4. Improve diagnosis and management of compartment syndromes
   5. Fractures in the elderly
      a. Peri-injury inpatient management, and rehabilitation
      b. Decrease mortality rate
      c. Elucidate pathways leading to restoration of independent living
      d. Improved systems management for common fractures, such as hip fractures

E. *Complications of Fractures*
   1. Improve treatment of skeletal infection with local measures and systemic adjuncts
      a. Further determine the relationship deformities and outcomes
      b. Develop and evaluate the effectiveness of bone graft substitute

F. *Rehabilitation and Workplace / Activity Re-entry*: Determine benefits of physical / occupational therapy protocols

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

G. *Outcomes and Economic Issues*:
   1. Further elucidate outcomes of specific injuries
      a. Patient-based outcomes
      b. Societal cost of injury
      c. Investigate impact of rehabilitation strategies
   2. Cost effectiveness of management options
      a. Optimize management to improve
      b. Assess time out of work
      c. Assess ability to return to same job
      d. Identity job modification techniques
      e. Evaluate occupational therapeutics

IV. REFERENCES

Barrett J, Baron J, Karagas M, Beach M: Fracture risk in the US Medicare population. *J Clin Epidemiol* 1999; 52:243-249.

Bone L, Johnson K, Weigelt J, Scheinberg R: Early versus delayed stabilization of femoral fractures: A prospective randomized study. *J Bone Joint Surg Am* 1989; 71:336-340.

Bosse M, MacKenzie E, Kellam J, et al: A prospective evaluation of the clinical utility of the lower-extremity injury-severity scores. *J Bone Joint Surg Am* 2001; 83:3-14.

Botha A, Moore F, Moore E, et. al.: Postinjury neutrophil priming and activation: An early vulnerable window. *Surgery* 1995;118:358-365.

Cummings S, Black D, Thompson, D, et al: Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Result from the Fracture Intervention Trial. *JAMA* 1998;280:2077-2082.

Geesink R, Hoefnagels N, Bulstra S: Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. *J Bone Joint Surg Br* 1999;81:710-718.

Giannoudis P, Smith R, Bellamy M, et. al.: Stimulation of the inflammatory system by reamed and unreamed nailing of femoral fractures: An analysis of the second hit. *J Bone Joint Surg Br* 1999;81:356-361.

Heckman J, Ehler W, Brooks B, et al: Bone morphogenetic protein but not transforming growth factor-beta enhances bone formation in canine diaphyseal nonunions implanted with a biodegradable composite polymer. *J Bone Joint Surg Am* 1999;81:1717-1729.

Kenwright J, Gardner T: Mechanical influences on tibial fractures healing. *Clin Orthop* 1998;355(suppl):179-190.

Koval K, Maurer S, Su E, Aharonoff G, Zucherman J: The effects of nutritional status on outcome after hip fracture. *J Orthop Trauma* 1999;13:164-169.

Matsen S, Malchow D, Matsen F III: Correlations with patients' perspectives on the result of lower-extremity amputation. *J Bone Joint Surg Am* 2000;82:1089-1095.

McFarland J: Perioperative blood transfusions: Indications and options. *Chest* 1999; 115(suppl):113S-121S.

Nowotarski P, Turen C, Brumback R, Scarboro J: Conversion of external fixation to intramedullary nailing for fractures of the shaft of the femur in multiply injured patients. *J Bone Joint Surg Am* 2000;82:781-788.

Ogura H, Tanaka H, Koh T, et al: Priming, second-hit priming, and apoptosis in leukocytes from trauma patients. *J Trauma* 1999;46:774-783.

Rauch F, Lauzier D, Croteau S, et. al.: Temporal and spatial expression of bone morphogenetic protein-2, 4, and 7 during distraction osteogenesis in rabbits. *Bone* 2000;27:453-459.

Scalea T, Scott J, Brumback R, et al: Early fracture fixation may be "just fine" after head injury: No difference in central nervous system outcomes. *J Trauma* 1999;46:839-846.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

V. PANEL MEMBERS

Chair:	Peter Trafton, MD	Brown University	Providence, RI
Co-chair:	Paul Tornetta, MD	Boston Medical Center	Boston, MA
	Michael J. Bosse, MD	Carolina Medical Center	Charlotte, NC
	Andrew R. Burgess, MD	University of Maryland Hospital	Baltimore, MD
	Thomas Decoster, MD	University of New Mexico Medical School	Albuquerque, NM
	Thomas Einhorn, MD	Boston Medical Center	Boston, MA
	Kenneth Johnson, MD	Vanderbilt University Medical Center	Nashville, TN
	Alan L. Jones, MD	UT Southwestern Medical Center	Dallas, TX
	Ellen MacKenzie, PhD	Johns Hopkins Bloomberg School of Public Health	Baltimore, MD
	James Nepola, MD	University of Iowa Hospital	Iowa City, IA
	Allan Tencer, PhD	University of Washington Medical Center	Seattle, WA

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel III: Upper Extremity: Microvascular, Nerve, and Tendon Research

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*

"No serious account of human life can ignore the central importance of the human hand." (Wilson)

The hand is a critical part of nearly every conceivable human activity. Its loss, or loss of the function of the upper limb which positions it, results in devastating impairment to all activities of daily living. It should not be surprising, therefore, that there has been considerable research involving conditions that result in hand impairment, and treatments to ameliorate that impairment. Nonetheless, large deficits remain in our understanding of both pathology and therapeutics of hand disorders. Some of these issues: arthritis, fractures, and cumulative trauma disorders, are covered elsewhere in this document. Those affecting nerves, tendons, and microvasculature are covered here.

B. *Importance to Public Health*

The hand is the most commonly injured human body part. In 1995, hand injuries and other disorders resulted in over 100 million days of lost or limited work and over 25 million medical office visits each year in the U.S., with a direct cost of at least $19 billion (Kelsey).

II. RECENT ADVANCES

A. *Peripheral Nerve Compression Syndromes*

Although the pathophysiology of nerve compression has been studied extensively, this remains a major problem, especially in the upper limb. Carpal tunnel syndrome is the most commonly operated problem in the upper limb, and represents a major source of disability. It is extremely common; prevalence studies suggest that it affects roughly 5% of the population at any one time (Atroshi), with the cumulative lifetime risk probably 2 or 3 times as high. There is a gender discrepancy and its basis is not well understood; CTS is 2 to 3 times as common in women as it is in men. The prevalence of CTS is related to a variety of risk factors, including not only gender but also age, obesity, smoking, and certain occupations. At particularly high risk are those from age 45 to 55 years who are obese, smoke, and whose job requires highly repetitive forceful grip with the wrist flexed, or who use undampened vibrating tools such as chippers or grinders for many hours per day.

While the treatment of CTS changed significantly in the 1990s, progress has been harder to quantify. There are still no relevant animal models, and clinical research has foundered on the issue of case definition, specifically whether changes in nerve conduction velocity and amplitude are necessary to confirm a diagnosis, or whether the diagnosis can be made on clinical grounds alone. Devices to perform carpal tunnel release (CTR) through a small incision, usually with endoscopic assistance, have been developed and have seen widespread use in the past decade, although recently there appears to be a trend back to open surgical release. The main benefit of CTR performed with endoscopic assist is a more rapid return of grip strength in the first few weeks after surgery, but this is counterbalanced with higher failure and complication rates. More fundamentally, the pathogenesis of CTS remains unclear. While the earliest pathological changes, of non-inflammatory synovial fibrosis, are well known, what induces these changes and how they affect nerve function remains to be elucidated.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

B. *Microvascular*

Beginning with the first upper limb reattachment in 1962, microsurgical reconstruction of the upper extremity has been progressively refined. The role and utility of the techniques in upper limb reconstruction is well established. Problems of microcirculation continue to affect outcomes, however. These may be associated with collagen vascular disorders, such as scleroderma, but may also be associated with devascularizing injuries or chronic regional pain syndromes.

Microsurgical reconstruction of soft tissue defects has the advantage of providing coverage in a single stage with very high success rates. Literally dozens of donor sites with surgically accessible vascular pedicles have been identified, including many local sources within the upper limb. In addition, vascularized, neurotized free muscle flaps now allow reanimation in some of brachial plexopathy or ischemic contracture. Vascularized joint transfers may occasionally be indicated for reconstruction of an isolated injury to the MCP or PIP joints, especially in children, where the transfer of an epiphysis permits growth of the transferred part. Microsurgical reconstruction using toe-to-hand transfers has become the optimal technique for reconstruction of the thumb and digits, most often after traumatic amputation, but occasionally also for reconstruction of congenital loss. The most recent advances have permitted the transfer of toe parts, so that a portion of the toe remains in situ. Especially for the great toe, partial toe transfers can minimize the impact of toe loss on weight bearing. Studies of microcirculation have also expanded our understanding of the factors affecting both nutritional and thermoregulatory flow. (Ruch)

C. *Transplantation*

Long a dream, the possibility of cadaveric hand transplantation has been opened in the past decade by recent advances in immunosuppression. Everyone involved emphasize that the issues to be addressed are not only biological but also ethical. (Brenner)

Basic research on limb transplantation has investigated the use of the newer immunosuppressive agents FK-506 (Tacrolimus) and RS-61443 (Mycophenolate mofetil) in small animals (rats). In these animal models, long term survivors have usually succumbed to overwhelming infection due to prolonged immunosuppression or due to graft-versus-host disease. Nevertheless, both unilateral and bilateral transplantations have been performed, with cases reported from the US, France, Austria, and China. Most have limited function to date, but except for the first patient, who requested reamputation, the initial experience appears favorable from the perspective of the patients and surgeons. (Jones)

D. *Tendon*

Tendon injuries to the hand and wrist are not common, but the results can often be devastating, as the injuries typically occur in young, active people, and current treatment takes many months to yield, on average, a good but not normal hand.

There have been many strides made in the improvement of tendon surgery. Technically, research has focused on improving the strength of repair constructs, minimizing friction, and modifying rehabilitation improving the ability of the repaired tendon to glide within the digit, and on understanding the role of growth factors and lubrication in tendon healing. These have strengthened the scientific basis for tendon repair and rehabilitation, but despite these advances, results remain less than perfect in most cases. (Boyer)

E. *Peripheral Nerve Trauma/ Brachial Plexus*

Traumatic injuries to peripheral nerve are uncommon. Nerve suture, first reported two centuries ago, has seen modest advancement, because until recently the focus of research was on the delicacy of the technique and the accuracy of the coaptation. Recent research suggests, however, that the impact of technique on outcome is small, with the largest impact on outcome by far being the patient's own innate neurological plasticity (Lundborg). Brachial plexus injuries are rare but devastating, as they occur primarily in neonates and young adults,

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

and frequently result in paralysis of an entire arm. Until recently, treatment was primarily palliative.

The mainstay surgical techniques have been reinvigorated in recent years by the use of specialized tubes to guide the nerve repair. Growth factors have been incorporated in the tubes to further stimulate nerve regrowth, but even with these advances the final result is still often an abnormal nerve. (Dahlin)

The past decade has seen significant advances, in more accurate prognostic assessment, in the reconstruction of the injured nerves, in the innovative use of uninjured nerves to "neurotize" the affected area, and in the use of microsurgical techniques to reconstruct the function of paralyzed muscles. (Songcharoen)

III. FUTURE DIRECTION OF RESEARCH

A. *Peripheral Nerve Compression*
   1. Increase understanding of the causes of peripheral nerve compression
   2. Develop relevant animal models
   3. Develop alternatives to surgical treatment

B. *Microvascular*
   1. Expand the role of prefabricated engineered tissue in free tissue transfer
   2. Identify the links, if any, between factors that regulate microcirculation and those which mediate pain perception

C. *Transplantation*
   1. Improved methods for addressing the tissue rejection phenomenon
   2. Consensus on ethical issues

D. *Tendon*
   1. Increase basic understanding of tendon healing
   2. Development of mechanisms to block the formation of tendon adhesions
   3. Development of artificial tendon materials
   4. Develop genetically engineered cells on collagen matrices to exactly reproduce the function of damaged tendons
   5. Development of methods for delivering growth factors to injured tendon
   6. Development of biologically active implants to speed tendon healing

E. *Peripheral Nerve /Brachial Plexus Injury*
   1. Research on regeneration of peripheral nerves, especially the effect of growth factors targeted to motor and sensory fascicles
   2. Identification of factors to speed nerve regeneration
   3. Research on regeneration of spinal nerves, especially the effect of growth factors targeted to motor and sensory fascicles
   4. Development of neural prostheses

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

IV. REFERENCES

Atroshi I, Gummesson C, Johnsson R, et. al.: Prevalence of carpal tunnel syndrome in a general population. *JAMA* 1999;282(2):153-158.

Boyer MI, Gelberman RH, Burns ME, et. al.: Intrasynovial flexor tendon repair. An experimental study comparing low and high levels of in vivo force during rehabilitation in canines. *J Bone Joint Surg* 2001;83-A(6):891-899.

Brenner MJ, Tung TH, Jensen JN, Mackinnon, SE: The spectrum of complications of immunosuppression: Is the time right for hand transplantation? *J Bone Joint Surg Am* 2002;84:1861-1870.

Dahlin LB, Anagnostaki L, Lundborg G: Tissue response to silicone tubes used to repair human median and ulnar nerves. *Scandinavian Journal of Plastic & Reconstructive Surgery & Hand Surgery.* 2001;35(1):29-34.

Jones JW, Gruber SA, Barker JH, Breidenbach WC: Successful hand transplantation: One-year follow-up: Louisville Hand Transplant Team. *New England Journal of Medicine* 2000;343(7):468-473.

Kelsey J, et al: *Upper Extremity Disorders*, New York, NY, Churchill Livingston, 1997, pp 1-3.

Lundborg G: A 25-year perspective of peripheral nerve surgery: Evolving neuroscientific concepts and clinical significance. [Review] *Journal of Hand Surgery - American Volume.* 2000;25(3):391-414.

Ruch DS, Smith TL, Smith BP, et. al.: Anatomic and physiologic evaluation of upper extremity ischemia. *Microsurgery* 1999;19(4):181-188.

Songcharoen P, Wongtrakul S, Mahaisavariya B, Spinner RJ: Hemi-contralateral C7 transfer to median nerve in the treatment of root avulsion brachial plexus injury. *Journal of Hand Surgery - American Volume.* 2001;26(6):1058-1064.

Wilson FR, *The Hand*, New York, NY, Random House, 1998, p 7.

V. Panel Members

Chair:	Daniel Mass, MD	University of Chicago	Chicago, IL
	Peter Amadio, MD	Mayo Clinic	Rochester, MN
	Mark E. Baratz, MD	Allegheny Ortho Association	Pittsburgh, PA
	Allen T. Bishop, MD	Mayo Clinic	Rochester, MN
	Joseph P. Iannotti, MD, PhD	The Cleveland Clinic	Cleveland, OH
	Neil Jones, MD	University of California, Los Angeles	Los Angeles, CA
	Ken Yamaguchi, MD	Washington University	St. Louis, MO

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Panel IV: Aging, Injury and Disability, Cartilage Structure and Function

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Cartilage injury and disorders cover a wide variety of clinical specialties, with treatments for traumatic injuries to cartilage and injury- or age-induced cartilage degeneration the most prevalent conditions. Treatments to repair injured or degenerated cartilage include stimulation of cartilage repair by microfracture, cartilage plugs replacing highly damaged cartilage, and replacement of cells by arthroscopy or cartilage implantation. At the extreme stage of degeneration or injury, joint replacement is performed.

B. *Importance to Public Health*
Cartilage is a vital component of joint structure, and critical for optimum functioning of any joint. It is estimated that more than one-half of persons will suffer from cartilage degeneration after the age of 60, resulting in reduce quality of life and significant loss of work time. Understanding the development and cause(s) of cartilage degeneration in osteoarthritis as the development of treatments to reverse or halt the progression of degeneration are priority concerns when establishing health policy goals for the next decade. Areas of focus include determining whether cartilage degeneration is a cause or result of osteoarthritis, and the role changes in subchondral bone stiffness and overall joint mechanics with their resultant abnormalities have in the degeneration of cartilage.

C. *Research Significance*
To meet the needs of understanding and treating cartilage damage, a research agenda must be diverse, and include basic understanding of the cell and molecular biology of cartilage development and growth, as well as understanding of the biomechanical function of this tissue. These concepts can then be applied to research and understanding of the pathogenesis of cartilage degeneration, the sequelae of cartilage injury, and the natural consequences of “wear and tear” in aging.

II. RECENT ADVANCES

A. *Total Joint Replacement (TJR)*
TJR has been acclaimed as the greatest surgical advance in the past three decades. By any outcome measure it has increased quality of life relative to cost to a greater extent than any other intervention. It also has kept many elderly people mobile and self-sufficient, rather than crippled by arthritis and dependent on institutional care.

B. *Sports Injuries*
Arthroscopy has converted the treatment of injuries like meniscus and ligament tears from costly inpatient surgery to cost-effective outpatient care. Many injuries of the professional athlete, the youthful amateur athlete, and the elderly sports enthusiast that previously halted activity are now managed successfully using less invasive procedures that often preserve rather than destroy structures.

C. *Rehabilitation of Joint Structures*
Concepts of early motion and passive motion have been shown to aid healing responses of bone and joint structures, shorten rehabilitation time, and return function to the injured joint.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

D. *Genetic Diseases*
We now realize that there is an inherited, but often complex, component to many musculoskeletal diseases, such as osteoarthritis, as well as the more straightforward genetic diseases.

E. *Molecular Biology and Gene Therapy*
The tools of molecular biology and gene therapy are now available but must be employed to develop and deliver products to replace bone and stimulate healing of joint surface defects, refractory cases of fracture nonunion, and tendon and ligament injuries.

F. *Cartilage Injury, Repair, and Osteoarthritis*
Several techniques including microfracture, tissue culture of chondrocytes, and "plug" replacement are being studied to understand their impact on local cartilage. The potential to stimulate cartilage repair or build new cartilage from multipotent stem cells would revolutionize the field of cartilage repair. Autologous cells could be used to replace damaged tissue.

G. *Cartilage Degradation*
It has been recently discovered that the major proteoglycan in cartilage, aggrecan, is turned over by a new class of enzymes, the aggrecanases. One family of enzymes, the ADAMTS family, are currently known to be central players in extracellular matrix (ECM) metabolism in cartilage and other tissues. Further research into their properties and the potential identification of additional enzymes can further our knowledge about cartilage degradation.

H. *Therapeutic Targets*
The TNF/ IL-1 pathways have been found to be of vital importance in inflammation and degradation in rheumatoid arthritis and are key therapeutic targets in the prevention of cartilage destruction in rheumatoid arthritis. These agents, along with the discovery of additional cytokines that may also influence inflammation and degradation, are strong candidates in developing approaches to osteoarthritis.

I. *Effect of Loading on Cartilage*
New information on the role of mechanical stimulation of cartilage and its role in chondrogenesis will help shed light on cartilage matrix synthesis.

J. *Not All Joints are Created the Same*
Different joints are affected by joint disease at different rates. The molecular basis for this has been studied particularly comparing the ankle and knee joint cartilage. Ankle joints have a different structure and a different complement of cell surface receptors. These differences could have a protective effect on the ankle cartilage.

III. FUTURE DIRECTION OF RESEARCH

A. Tissue Engineering
1. Tissue engineering of cartilage
2. Capacity of cartilage to repair and for repair to be stimulated
3. Growth factor signaling in cartilage

B. *Genetic Research/Biomarkers*
1. Genetics of cartilage predisposition to injury and degenerative disease (candidate genes, risk prediction)
2. Biomarkers of OA
   a. Prevention of OA via nitric oxide blockers
   b. Imaging of cartilage in the normal joint and in the osteoarthritic joint
3. Chondrocyte-matrix interactions
4. Chondrogenesis from stem cells

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

C. *Cell Biology Research*
   1. Molecular basis (pathogenesis) of osteoarthritis
   2. Molecular basis (pathogenesis) of osteochondritis

D. *Injury Repair*
   1. Understanding of growth plate biology and injury repair
   2. Cartilage response to injury including release of factors and matrix degradation products
      a. Mediation of cartilage inflammation
      b. The role of Pro-inflammatory cytokines in osteoarthritis
      c. The roles of glucosamine and chondroitin sulfate in cartilage metabolism

E. *Biomechanics and Biophysics*
   1. Pathomechanics of traumatic injury to cartilage
   2. Mechanical properties of cartilage implants
   3. Animal models of joint injury

F. *Osteoarthritis*
   Metabolic changes in cartilage preceding and accompanying osteoarthritis
      a. Degradative enzymes
      b. Apoptosis
      c. Proliferation and anabolic events

G. *Gender Variations*
   Sex hormone effects on chondrocyte function

H. *Impacts of Aging*
   Phenotypic changes in cartilage with aging

IV. REFERENCES

Blunk T, Sieminski AL, Gooch KJ, et. al.: Differential effects of growth factors on tissue-engineered cartilage. *Tissue Eng* 2002;8(1):73-84.

Cho JY, Grant TD, Lunstrum GP, Horton WA: Col2-GFP reporter mouse—A new tool to study skeletal development. *Am J Med Genet* 2001;106(4):251-253.

Cho TJ, Gerstenfeld LC, Einhorn TA: Differential temporal expression of members of the transforming growth factor beta superfamily during murine fracture healing. *J Bone Miner Res* 2002;17(3):513-520.

Chung UI, Schipani E, McMahon AP, Kronenberg HM: Indian hedgehog couples chondrogenesis to osteogenesis in endochondral bone development. *J Clin Invest* 2001;107(3):295-304.

Close DR: Matrix metalloproteinase inhibitors in rheumatic diseases. *Ann Rheum Dis* 2001;60 Suppl 3:iii62-67.

de Crombrugghe B, Lefebvre V, Nakashima K: Review: Regulatory mechanisms in the pathways of cartilage and bone formation. *Curr Opin Cell Biol* 2001;13(6):721-727.

Doege KJ, Hall LB, McKinnon W, Chen L, Stephens DT, Garrison K: A remote upstream element regulates tissue-specific expression of the aggrecan gene. *J Biol Chem* 2002;7.

Erickson GR, Gimble JM, Franklin DM, et. al.: Chondrogenic potential of adipose tissue-derived stromal cells in vitro and in vivo. *Biochem Biophys Res Comm* 2002;290(2):763-769.

Eyre D: Collagen of articular cartilage. *Arthritis Res* 2002;4(1):30-35.

Farmer JM, Martin DF, Boles CA, Curl WW: Review: Chondral and osteochondral injuries: Diagnosis and management. *Clin Sports Med* 2001;20(2):299-320.

Fukui N, Purple CR, Sandell LJ: Review: Cell biology of osteoarthritis: the chondrocyte's response to injury. *Curr Rheumatol Rep* 2001;3(6):496-505.

Guilak F, Butler DL, Goldstein SA: Functional tissue engineering: The role of biomechanics in cartilage repair. *Clin Orthop Rel Res* 2001;391:S295-S305.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

Hanada K, Solchaga LA, Caplan AI, et. al.: BMP-2 induction and TGF-beta 1 modulation of rat periosteal cell chondrogenesis. *J Cell Biochem* 2001;26;81(2):284-294.

Izzo MW, Pucci B, Tuan RS, Hall DJ: Gene expression profiling following BMP-2 induction of mesenchymal chondrogenesis in vitro. *Osteoarthritis Cartilage* 2002;10(1):23-33.

Korhonen RK, Wong M, Arokoski J, et. al.: Importance of the superficial tissue layer for the indentation stiffness of articular cartilage. *Med Eng Phys* 2002;24(2):99-108.

Lefebvre V, Behringer RR, de Crombrugghe B: L-Sox5, Sox6 and Sox9 control essential steps of the chondrocyte differentiation pathway. *Osteoarthritis Cartilage* 2001;9 Suppl A:S69-75.

Majumdar MK, Wang E, Morris EA: BMP-2 and BMP-9 promotes chondrogenic differentiation of human multipotential mesenchymal cells and overcomes the inhibitory effect of IL-1. J *Cell Physiol* 2001;189(3):275-284.

Mauck RL, Soltz MA, Wang CC, et. al.: Functional tissue engineering of articular cartilage through dynamic loading of chondrocyte-seeded agarose gels. *J Biomech Engng* 2000;122:252-260.

Noth U, Tuli R, Osyczka AM, Danielson KG, Tuan RS: In vitro engineered cartilage constructs produced by press-coating biodegradable polymer with human mesenchymal stem cells. *Tissue Eng* 8(1):131-144.

Pelletier JP, Jovanovic DV, Lascau-Coman V, et. al.: Selective inhibition of inducible nitric oxide synthase reduces progression of experimental osteoarthritis in vivo: Possible link with the reduction in chondrocyte apoptosis and caspase 3 level. *Arthritis Rheum* 2000;43:1290-1299.

Poliard A, Blumen B, Freyria AM, et. al.O: Review: Chondrogenesis from stem cell recruitment to hypertrophy by a tripotential mesoblastic cell line. *Osteoarthritis Cartilage* 2001;9 Suppl A:S85-90.

Ruane R and Griffiths P: Glucosamine therapy compared to ibuprofen for joint pain. *Br J Community Nurs* 2002;7(3):148-152.

Sarkar S, Petiot A, Copp A, Ferretti P, Thorogood P: FGF2 promotes skeletogenic differentiation of cranial neural crest cells. *Development* 2001;128(11):2143-2152.

Sekiya I, Colter DC, Prockop DJ: BMP-6 enhances chondrogenesis in a subpopulation of human marrow stromal cells. *Biochem Biophys Res Commun* 2001;8;284(2):411-418.

Shum L, Nuckolls G: The life cycle of chondrocytes in the developing skeleton. *Arthritis Res* 2002;4(2):94-106.

Spagnoli A, Torello M, Nagalla SR, et. al.: Identification of STAT-1 as a molecular target of insulin-like growth factor binding protein-3 (IGFBP-3) in the process of chondrogenesis. *J Biol Chem* 2002;8.

Tortorella MD, Burn TC, Pratta MA, et al: Purification and cloning of aggrecanase-1: A member of the ADAMTS family of proteins. *Science* 1999;284:1664-1666.

Unger S, Hecht JT: Pseudoachondroplasia and multiple epiphyseal dysplasia: New etiologic developments. *Am J Med Gene* 2001;106(4):244-250

V. PANEL MEMBERS

Chair:	Linda J. Sandell, PhD	Washington University	St. Louis, MO
Co-chair:	David Eyre, PhD	University of Washington	Seattle, WA
	Kenneth D. Brandt, MD	Indiana Univ School of Medicine	Indianapolis, IN
	Joseph A. Buckwalter, MD	Univ of Iowa Hospitals	Iowa City, IA
	Seth Greenwald, PhD	Ortho Research Lab/Lutheran Hospital	Cleveland, OH
	Farshid Guilak, PhD	Duke Univ Medical Center	Durham, NC
	Klaus E. Kuettner, PhD	Rush Presbyterian St. Lukes	Chicago, IL
	Stefan Lohmander, MD	Lund University Hospital	Lund, Switzerland
	Van C. Mow, PhD	Columbia University	New York, NY
	A. Robin Poole, PhD	Shriners Hospital	Montreal, Canada

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Panel V: Tissue Engineering

I. DESCRIPTION OF SCOPE

A. *Tissue Engineering Defined*

Tissue engineering can be defined as any effort to repair, augment, replace or regenerate a specific tissue in a specific anatomic location. Modern tissue engineering includes traditional applications of "biologically inert" materials, such as metal alloys, ceramics, and polymers. However, it expands upon conventional strategies through the development and use of "biologically active" materials, surfaces, and bioactive compounds using a cell-based strategy. The tissues of particular interest and value to the field of orthopaedic surgery and musculoskeletal medicine are bone, cartilage, tendon, ligament, meniscus, intervertebral disc, fat, muscle, and nerve. The repair, augmentation, replacement or regeneration of these tissues are of central importance to every specialty and subspecialty in orthopaedic surgery and also interface with a broad range of other specialties, including neurosurgery, plastic surgery, vascular surgery, general surgery, ENT, dentistry, and maxillofacial surgery.

B. *Tools Of Tissue Engineering*

Cells with pleuripotential capabilities are present as pools of adult stem cells and progenitor cells in almost all healthy adult tissues, and can be exploited to generate new tissue, forming the basis for Cellular Therapies in Tissue Engineering.

The ability of stem cells and progenitor cell pools to function effectively depends upon many factors. These factors include: the number of stem cells and progenitors present in the tissue or region in which tissue is desired, the intrinsic biologic properties and potential of these cells, and important chemical and physical stimuli present in the local cellular environment. Cells interact with an environment containing complex sets of biological, chemical, and physical stimuli, as well as essential chemical substrates and nutrients (e.g. oxygen, glucose, vitamins). This environment in turn is dependent on the function of other resident or infiltrating cells (mature cells and possibly of other progenitor populations) that may be present in the tissue region.

C. *Stem Cell and Progenitor Cell Populations*

Tissue sources include bone marrow, periosteum, peritrabecular soft tissues, cartilage, muscle, fat, and vascular pericytes. Many names have been used to describe cells with these intrinsic properties, including: fibroblastic colony-forming units (CFU-F), mechanocytes, bone marrow stromal cells, mesenchymal stem cells, and adult multipotential progenitor cells, although the precise definition and biologic capabilities ascribed by these terms are not entirely synonymous. The term connective tissue progenitor has been proposed as a generally applicable term for any proliferative cell population that is capable of differentiating into one or more connective tissue phenotypes. The heterogeneity within the population of adult tissue-derived stem cells and progenitors, the organizational hierarchy of these cell populations, and the full range of intrinsic biologic behavior and potential is only beginning to be understood.

D. *Tissue Engineering Strategies*

1. *In Vivo Targeting existing stem cells and progenitor cells in a tissue or region.*

   This strategy requires that the region of interest either already includes a sufficient population of stem cells and progenitors, or that the intervention may cause these cells to be recruited to migrate into the region where new tissue is desired. These targeting strategies include a variety of means intending to positively influence the activation, migration, proliferation, differentiation, and survival of stem cells and progenitor cells *in situ*, resulting in the formation of the preferred functional tissue. Examples include: implantation of acellular tissue scaffolds (e.g. allograft matrices, hydroxyapatite, fibrin,

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

hyaluronic acid, and synthetic polymers); the use of locally applied growth factors (e.g. BMPs or FGF-2); the use of biophysical stimulation, such as mechanical loading or application of electromagnetic field stimulation; and even pharmacologic strategies, such as systemic administration of trophic pharmaceuticals and bioactive molecules that may act directly upon the stem cell and progenitor cell population (e.g. PTH, estrogen used in treatment of osteoporosis, or Growth Hormone-induced increase in muscle mass). Growth factors may be delivered as purified or recombinant proteins or via cells genetically engineered to over express a particular factor of interest.

2. *In Vivo transplantation of stem cells and progenitor cells into a tissue or region.*
   This strategy may utilize a number of different means to accomplish one or more of three primary goals: 1) to obtain a sufficient or optimal number of stem cells and progenitors; 2) to augment or modify the intrinsic biological potential of the stem cells and progenitors that are available for local or systemic transplantation; and 3) to optimize the survival and biological performance of transplanted cells.

   Some common examples of this strategy include whole tissue transplantation, for example: the harvest of cancellous or cortical bone autograft; transplantation of bone marrow harvested by aspiration; autograft or allograft cartilage transplantation; tendon transplantation; nerve grafting; vascularized flaps (free or pedicle based) containing bone, muscle, tendon, ligament, nerve, cartilage, fat or skin; and avascular skin grafts (split or full thickness).

   Isolation and physical manipulation of stem cells and progenitors. Stem cells and progenitor cell populations that can generate new musculoskeletal tissues can now be isolated from bone, bone marrow, fat, muscle, and perivascular cells called pericytes. The cells obtained from these tissues using methods for cell concentration and selection, including: density separation by centrifugation, selection based on parameters of size or morphology, and selection based on expression of specific surface markers (e.g. antibody mediated panning or affinity column, or fluorescent activated cell sorting [FACS] devices).

3. *Ex Vivo Tissue Generation and Transplantation*
   This strategy involves generation of fully organized and mature tissue outside of the body, and then transplantation of the formed tissue into the anatomic site where it is prepared to function as needed. This is often the first vision that the general public has of tissue engineering. However, this strategy is also the most complex and challenging. It may be desirable in only a small fraction of clinical situations. The four great challenges of this strategy are: 1) To generate functional tissues that are both biologically healthy and sustainable, 2) To generate functional tissues that possess the physical properties required to replace normal tissues, 3) To transplant the new tissue into the body in a way that the cells in the new tissue continue to survive, and 4) To implant the new tissue in a way that it will physically integrate both biologically and mechanically with surrounding tissue to provide normal function.

E. *Tissue Scaffolds for Tissue Engineering*

In addition to stem cells and progenitor cells, Tissue Scaffolds are a central tool of Tissue Engineering. Implanted tissue scaffolds can provide support for cell attachment and migration of targeted cells in adjacent tissues, and provide the means of controlling and guiding the distribution of these cells in three dimensions. Tissue scaffolds can be used to define and modify the biological, chemical and biophysical environment presented to a cell, inducing targeted cells to form a functional replacement tissue. Tissue scaffolds may also be seeded with cells prior to implantation.

Further development of biomaterials for use as scaffolds for tissue engineering applications. Broadly, these fall into three categories: 1) biologically derived polymers (e.g., collagen, hyaluronan, fibrin matrices); 2) ceramics or mineral-based matrices; and 3) synthetic biomaterials (e.g., poly(glycolic acid), poly(lactide), poly(caprolactone) and varying co-

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

polymers). The biological activity of tissue scaffolds can be modified by presentation or release of bioactive compounds (e.g., cell ligands or adhesion molecules, growth factors, drugs, or other pharmacologic agents) or drug delivery systems (e.g., antibiotics, growth factors). They can also be modified by changes in the chemical surface (e.g., hydroxyapatite coating) surface topography (e.g. roughness, microscopic texture or patterning).

II. RECENT ADVANCES

A. *Stem Cell Biology*
1. Discovery and recognition of multiple multipotent adult stem cell populations in
2. bone marrow and other tissues.
3. Discovery and characterization of Embryonic Stem Cells
4. Characterization of activating signals for human bone marrow derived stem cells

B. *Cell Biology*
1. Characterization of pathways regulating apoptosis in bone and bone marrow derived cells.
2. Characterization of nuclear transcription factors and developmental regulators of patterning and differentiation

C. *Materials Science*
1. New approaches to create hybrid polymeric materials with a wide range of physical properties
2. Development of novel techniques to polymerize scaffolds in situ
3. Advanced a new understanding of how specific biopolymers (e.g., hyaluronan, collagen) influence cellular biology
4. Development of injectable materials as bulk tissue replacements and to deliver cells and growth factors
5. New techniques to modify surfaces to enhance cellular adhesion and control cellular behavior

D. *Growth Factor – Cytokine Biology*
1. Availability of purified human recombinant protein growth factors in large quantity for In vitro and in vivo experimentation.
2. Isolation and purification of multiple bone morphogenetic proteins (BMPs) and Growth and Differentiation Factors (GDFs) in humans and other vertebrates.
3. Demonstration of safety and efficacy of BMP-2 and OP-1(BMP-7) in prospective clinical trials

E. *Biomechanics – Biophysics*
1. Characterization of the mechanical and physical signals relevant to cells within healthy tissues and material replacements.
2. Advanced use of mechanical and physical signals in bioreactor design to modify tissue growth ex vivo

F. *Genetic Engineering*
Development of non-replicating viral vectors with large insert capacity, high efficiency of gene transfection, and biologically silent reporter construct (e.g. green fluorescence protein [GFP]).

G. *Imaging*
1. Ability to image microscopic features of repair tissues (e.g., fiber architecture, chemical composition)
2. Ability to use imaging tools to evaluate joint contact patterns in vivo
3. Use of high resolution imaging techniques to characterize scaffold microarchitectures

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

H. *Sensor Technology*
Recognition of limiting biologic factors in tissue response around implanted biosensors (fibrous tissue response, protein deposition, local tissue inflammation)

III. Future Directions Of Research

A. *Stem Cell Biology*
1. Determination of the heterogeneity within the populations of adult tissue-derived stem cells, transit populations, and progenitors
2. Determination of the organizational hierarchy of stem cell populations
3. Determination of the full range of intrinsic biologic behavior and potential of stem cell populations
4. Determination of the modulators for stem cell activation, proliferation, migrations, differentiation, and survival
5. Identification of markers for stem cell populations, transit populations, and progenitors useful for in vitro and in vivo assay
6. Identification of markers for stem cell populations, transit populations, and progenitors useful for rapid concentration and selection of specific cell sets from heterogeneous populations.

B. *Cell Biology*
1. Knowledge of signaling pathways that control cellular proliferation, differentiation and survival in cells of mesenchymal origins (e.g., chondrocytes, osteoblasts/cytes, fibroblasts)
2. Basic knowledge of changes in protein/gene expression with disease states in native tissues, and following exposure to tissue scaffolds, exogenous cells, growth factors, gene therapy
3. Enhanced understanding of regulatory regions of genes relevant to musculoskeletal tissues

C. *Materials Science*
1. Ability to engineer scaffolds with complex, controlled architecture and targeted sets of physical and mechanical properties
2. Development of new surface modification strategies to promote cell adhesion, tissue integration and control cellular phenotype
3. Use of new micro- and nano-patterning technologies to create tissue scaffolds for control of cellular and molecular events
4. Use of recombinant technologies for control of materials design and synthesis

D. *Growth Factor – Cytokine Biology*
1. Improved delivery systems controlling conformation, presentation, concentration, delivery rate, bioavailability, and distribution of peptide growth factors and cytokines
2. Genetically engineered cytokines and growth factors with enhanced or more selective biologic properties than native molecules (binding affinity, receptor specificity, solubility, degradation, etc).

E. *Biomechanics - Biophysics*
1. Establish biomechanical and biophysical parameters of requirements for successful tissue-engineered replacements
2. Develop tissue scaffolds to recreate biomechanics and biophysics of native tissue
3. Advance knowledge of the mechanical and physical signals relevant to cells within healthy tissues and material replacements
4. Advance use of physical signals in bioreactor design to modify tissue growth ex vivo
5. Bioreactor technology controlling and simulating biological conditions of mass transport

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

F. *Imaging*
   1. Develop new modalities to image cellular morphology and chemistry in situ
   2. Advance use of imaging for noninvasive determinations of procedural outcome
   3. Development of quantitative imaging and computational methods for tissue analysis, to merge or combine information from 2D or 3D data sets (e.g. microCT, microMR, microPET, histomorphometry) in a single specimen.

G. *Sensor Technology*
   1. Chemosensitive fluorophors for fiberoptic sensors sensitive to glucose, oxygen, electrolytes and other key substrates.
   2. Fully implantable or percutaneous long-term miniature wireless chemical and biophysical sensors.

IV. REFERENCES

Boskey AL: Musculoskeletal disorders and orthopaedic conditions. *JAMA* 2001;285:619-623.

Griffith LG, Grodzinsky AJ: Advances in biomedical engineering. *JAMA* 2001;285:556-561.

Huard J, Fu FH (eds): *Gene Therapy and Tissue Engineering in Orthopaedic and Sports Medicine (Methods in Bioengineering)* by Basel, Switzerland, Birkhauser, 2000.

Hunziker EB: Articular cartilage repair: basic science and clinical progress, a review of the current status and prospects. *Osteoarthritis Cartilage* 2002;10(6):432-463.

Lanza RP, Langer R, Vacanti JP (eds): *Principles of Tissue Engineering,* [Ed 2]. San Diego, San Francisco, New York, Academic Press, 2000.

Muschler GF, Midura RJ: Connective tissue progenitors: Practical concepts for clinical applications. *Clinical Orthopaedics and Related Research* 2002;395:66-80.

V. PANEL MEMBERS

Chair:	George F. Muschler, MD	Cleveland Clinic Foundation	Cleveland, OH
	Michael G. Dunn, PhD	Robert Wood Johnson University Hospital	New Brunswick, NJ
	Robert E. Guldberg, PhD	Georgia Institute of Technology	Atlanta, GA
	Ernst Hunziker, PhD	University of Bern	Bern, Switzerland
	Lori A. Setton, PhD	Duke Univ Medical Center	Durham, NC

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel VI: Gene Therapy

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*

The sequencing of the human genome has changed the way we view disease and will enable clinicians to treat diseases in ways that were not possible in the past. The development of gene therapy has been an evolutionary process that began with the identification of the building blocks of life (DNA, RNA and transcription factors), the production of recombinant proteins, and the subsequent ability to deliver DNA to specific target cells. Advances in our understanding of the biological processes associated with developmental, degenerative, traumatic conditions, and cancer have allowed us to identify molecules that play a critical role in the signal transduction cascades that influence both normal and pathological cell processes.

The availability of recombinant growth factors will clearly have an impact on the treatment of a variety of musculoskeletal problems. However, the ability to either inhibit or stimulate intracellular signaling pathways holds the potential to treat diseases associated with gene mutations (i.e. osteogenesis imperfecta), and a variety of clinical problems which are either systemic (i.e. rheumatoid arthritis, other inflammatory diseases, and osteoporosis) or located at a specific anatomic site (i.e. fracture nonunion pseudarthrosis of the spine, cartilage repair, osteolysis around total joint arthroplasties, and tendon, ligament or muscle injuries).

B. *Importance to Public Health*

Gene therapy has the potential to revolutionize the treatment of a wide range of musculoskeletal problems that include gene mutations, developmental, degenerative, and traumatic conditions and cancer. Gene therapy strategies that are developed must be predictable, safe and cost effective.

II. RECENT ADVANCES

A. *Gene Transfer*

Over the past two decades methods of gene delivery have improved and now the delivery of specific genetic information to cells in vitro has become relatively routine. However, although there are over 300 gene therapy trials under way in the United States at this time, there is still no established FDA-approved gene therapy. Gene therapy has been used successfully in a variety of orthopaedic musculoskeletal-related preclinical models. Gene transfer has been used in animal models to enhance bone repair, fusion of the spine, tendon healing, and cartilage repair.

In addition, in a clinical trial in humans, gene therapy showed potential as a therapeutic agent to treat rheumatoid arthritis. The goal now is two fold: (1) Identify the subset of genes that are causative or directly related to disease processes in order to identify the molecules that can be used in gene transfer strategies and (2) identify the most efficacious and safe methods for gene delivery. A variety of viral and non-viral delivery methods are presently being investigated.

B. *Potential Failures—Patient Safety*

There already has been one well-documented death in a gene transfer trial that appeared to be at least partially related to a lack of protection for human subjects. Many of the patients that will be eligible for gene transfer treatment for musculoskeletal diseases will be relatively young and will not be suffering from life-threatening conditions. The goal will be to improve the quality of life and therefore safety will be more important than efficacy.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

III. Future and Directions of Research

A. *Musculoskeletal Genome*
Identify the subset of genes that encompass the musculoskeletal genome. Identify the genes that are causative or directly related to disease processes associated with the development of such conditions as rheumatoid arthritis, osteoarthritis, osteolysis, fracture healing, cartilage repair etc. (genetic counseling)

B. *Identify the Most Efficient and Safe Gene Delivery Mechanisms*
1. Investigation of viral and non-viral gene transfer strategies.
2. Identify new strategies to control protein expression by controlling promoter activity.

C. *In Vivo Promoter Control*
1. Identify novel promoters that can limit protein expression to specific cell
2. populations.
3. Use promoters to limit protein expression to different stages of cell
4. differentiation.
5. Develop promoters to combine pharmacology and gene therapy.
6. The use of agents that can be ingested to either inhibit or activate the expression of a particular protein can be delivered to cells by gene transfer (i.e. use an agent to turn off cells once bone repair has been enhanced in patients with osteoporosis.)

D. *Multiple Gene Delivery*
Deliver multiple genes to cells that are turned on and off at different times by promoter activation or inhibition.

E. *Gene Therapy and Tissue Engineering*
Develop strategies to supply genes to different materials that are implanted at specific anatomic sites, which would include the coating material with specific DNA that can be activated or with cells that have been genetically manipulated.

F. *Safety*
1. Our goals as clinicians and scientists should continually focus on the protection of human subjects.
2. Carefully evaluate the potential adverse effects of long-term gene therapy in appropriate animal models. There is a risk of viral replication and of stimulation of oncogenes that could jeopardize the overall health of patients.

IV. REFERENCES

Anderson WF: Human gene therapy. *Nature* 1992;392:25-30.

Evans CH, Ghivizzani SC, Kang R, et. al.: Gene therapy for rheumatic diseases. *Arthritis Rheum* 1999;42:1-16.

Evans CH, Ghivizzani SC, Herndon JH, et. al.: Clinical trials in gene therapy of arthritis. *Clin Orthop* 2000;S300-7.

Evans CH, Robbins PD: Potential treatment of osteoarthritis by gene therapy. *Rheum Dis Clin North Am* 1999;25:333-44.

Goomer RS, Deftos LJ, Terkeltaub R, et. al.: High efficacy non-viral transfection of primary chondrocytes and perichondrial cells for ex-vivo gene therapy to repair articular cartilage defects. *Osteoarthritis and Cartilage* 2001;9(3): 248-256.

Goomer RS, Maris T, Gelberman R, et. al.: Nonviral in-vitro gene therapy for tissue engineering of articular cartilage and tendon repair. *Clin Orthop* 2000;379S, S189-200.

Hannallah D, Peterson B, Lieberman JR, Fu FH, Huard J: Gene therapy in orthopaedic surgery. *J Bone Joint Surg Am* (in press).

Lander ES, et al: Initial sequencing and analysis of the human genome. *Nature* 2001;409:860-921.

Oakes DA, Lieberman JR: Osteoinductive applications of regional gene therapy: *ex vivo* gene transfer. *Clin Orthop* 2000:379S:101-112.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Puzas JE, O'Keefe RJ, Lieberman JR The orthopaedic genome: What does the future hold and are we ready? *J Bone Joint Surg Am* 2002;84:133-141.

Venter JC, Adams MD, et al: The sequence of the human genome. *Science* 2001;291:1304-1351.

V. PANEL MEMBERS

Chair:	Jay R. Lieberman, MD	University of California, Los Angeles	Los Angeles, CA
	David Amiel, PhD	University of California, San Diego	La Jolla, CA
	Chris Evans, PhD	Harvard University Medical School	Boston, MA
	Regis O'Keefe, M.D	University of Rochester Medical Center	Rochester, NY
	J. Edward Puzas, PhD	University of Rochester Medical Center	Rochester, NY
	Edward Schwarz, PhD	University of Rochester Medical Center	Rochester, NY

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel VII: Statistics and Outcomes Research

I. DESCRIPTION OF SCOPE

A. *Outcomes Research*

Outcomes research is a relatively new research approach that focuses on the effectiveness of medical care. One of the major factors leading to the outcomes research agenda was the research of Wennberg and Gittlesohn, the first to explore the issue of small area variations. By using large administrative population datasets, such as hospital discharge data and population-based analyses of the utilization of health care, they determined that the use and delivery of medical care differs dramatically across small geographic areas. While there is minimal variation for the treatment of hip fractures, for example, almost every other orthopaedic condition that has been studied has a wide treatment differential. Analyses have indicated that a major factor responsible for the variations is related to differences in physicians' recommendations for alternative treatments. The issue of small area variation has been a strong impetus for outcomes research.

The methodology of outcomes research is to focus on patient-oriented functional outcomes and the effectiveness of medical care. Other research methods in outcomes research include meta-analysis of the literature, the analysis of large databases and decision analyses. The four characteristics of clinical outcomes research studies include: 1) a focus on patient oriented assessments, 2) assessment of care in the community (not just academic) setting, 3) the use of large databases or populations and 4) the goal of promoting change in clinical practice by using the research findings to develop practice parameters or guidelines.

B. *Statistics*

While the statistical analyses of large databases may provide information on large numbers of patients, there are limitations. Databases are usually established for administrative purposes, not clinical research, and thus, limited information is available. Length of stay, readmission rates and complication rates may be available, but important information related to disease severity, comorbidities and patients' reports of outcome are not available. Database analysis has been used to investigate results of lumbar spine fusion and disk surgery, for example, and in evaluating the relationship between the volume of procedures performed and complication rates. National collaborative databases have also been constructed to study arthroplasty outcomes and compile results of implant retrieval.

The controlled trial remains the standard for clinical research as it is most efficient in limiting bias. This research is conducted under optimum circumstances where every aspect of the delivery of the treatment is standardized. Although very difficult to perform and expensive, recent successes in arthroplasty and spinal surgery trials have shown that the orthopaedic community can succeed in these worthwhile endeavors. Effectiveness research is the study of treatment done under the usual circumstances of care delivery such as in the community setting.

II. RECENT ADVANCES

A. *Questionnaire Development*

Outcomes research requires the collection of patient-oriented information. Questionnaires have been developed to determine patients' assessments of their physical and mental health, quality of life, and satisfaction with care. These questionnaires, in some cases, have been incorporated into large randomized clinical trials to maximize clinical utility of the research design.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

A questionnaire of health status needs to be: 1) validated, that is, measure what it is supposed to, 2) reproducible, that is, result in the same answer each time it is administered in the absence of a change in health status, and 3) responsive, that is, sensitive to clinically important changes. There are generic health measures that measure general function and quality of life. In addition, there are disease specific questionnaires that focus on a particular disease entity. The SF-36 is a well-validated measure of general health, but a disease-specific measure may show greater change in the treatment of orthopaedic conditions.

The AAOS in conjunction with COMSS has developed four patient-based, region-specific outcome instruments (questionnaires) for the spine, upper extremity, lower extremity, and for pediatric conditions. The questionnaires include: patient demographics, a comorbidity or comorbidity index, the SF-36 for adults, and an equivalent measure for pediatrics, as well as specific regional questions. Emphasis is on self-reported function. These questionnaires have been tested and validated in these four areas and are available for use in assessment of community-based practice. The Musculoskeletal Function Assessment (MFA) and the Short Musculoskeletal Function Assessment (SMFA) are comprehensive instruments which have been tested and validated for use in musculoskeletal conditions. As more use is made of these and other instruments to determine patient outcomes, we will have a better understanding of the effectiveness of orthopaedic care.

B. *Technological Advances*
Advances in computer software and hardware have created opportunities to move away from standard paper and pencil formats for data entry toward more efficient and accurate methods. Touch screen entry, scanners, hand-held peripheral devices and voice-interactive-response methodology have been tested and confirmed to be more efficient and accurate. These advances promise to enhance data collection in orthopaedists' offices while minimizing disturbances in the standard office patient flow.

III. FUTURE DIRECTION FOR RESEARCH

A. *Outcomes Data Collection*
Continue the development of state and regional orthopaedic clinician groups in order to collect clinical outcomes information and do effectiveness research. The Maine Medical Assessment Foundation is an excellent prototype for this work.

B. *Collaborative Clinical Trials*
Utilizing specialty societies, develop problem-oriented collaborative clinical groups to perform controlled trials of musculoskeletal interventions (operative and non-operative). Examples of early successes include the Orthopaedic Trauma Association and the Knee Society. The Pediatric Orthopaedic Society of North American developed a web-based clinical trials network that enables multiple centers to participate in both randomized clinical trials and prospective observational studies.

C. *Utilize the Burden of Disease*
Documentation of musculoskeletal burden of disease data being developed for the Bone and Joint Decade should be the single most important research effort for AAOS, and should be used to help set priorities based upon the impact of the population.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

D. *Study Underutilization of Orthopaedic Services*
Study the magnitude of and gain understanding of the reasons behind underutilization of orthopaedic services in the minority community.

E. *Prioritize Topics of High Clinical Importance*
The prioritization would be based on the degree of functional impact and variation in clinical practice.

F. *Academic Health Center Utilization*
Utilize the influence of academic health centers to improve the quality of clinical research and publication.

G. *Collaborative Research Efforts*
Work collaboratively with health care payers to facilitate studies as outlined in the first two items.

H. *Address Barriers to Developing Successful Outcomes Systems*
The technological barriers are being overcome, especially with new Web-based technology. The psychological barriers, including physician reluctance to share data, and the difficulty of demonstrating added value for participating physicians remains. Additional barriers to data collection may arise in conjunction with new federal regulations regarding data confidentiality, a consequence of the 1996 Health Insurance Portability and Accountability Act, otherwise known as HIPAA.

I. *Reduce Burden of Outcomes Data Collection*
Attempt to reduce physician burden of data collection and at the same time recognize that there are multiple end users of patient-based data. These end users include: physicians in quality improvement initiatives, accrediting bodies for credentialing, boards for maintenance of certification, and payers for accountability and choice. It must be recognized that the identical outcomes data can be used by the various end users for quite disparate purposes.

J. *Utilize Outcome Data to Educate Patients*
Encourage and further study the utilization of outcome data in educating patients to enhance their participation in decision making about treatment choices.

K. *Research Patient Characteristics that Impact on Outcomes*
Develop a greater understanding of which patient characteristics are associated with better and worse outcomes and how these risk factors may be mitigated.

L. *Standardize Diagnostic Criteria*
Develop standardized diagnostic criteria for orthopaedic conditions

M. *Create Performance Measures*
Using an evidence-based approach, develop performance measures for orthopaedic practice.

N. *AAOS/NIAMS Collaborative Clinical Trials*
Study the feasibility of establishing a clinical trials center in collaboration with NIAMS within the AAOS.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

IV. REFERENCES

Clark C, Heckman J: Volume versus outcomes in orthopaedic surgery; a proper perspective is paramount. *JBJS* 2001;83:1619-1621.

Freedman K and Berbstein J: Current concepts review: Sample size and statistical power in clinical orthopaedic research. *JBJS* 1999;81:1454-1460.

Hawker G, Wright J, Coyte P, et al: Health-related quality of life after knee replacement: Results of the knee replacement patient outcomes research team study. *JBJS* 1998;80:163-173.

Hunsaker F, Cioffi D, Amadio P, Wright J, Caughlin B: The American Academy of Orthopaedic Surgeons outcomes instruments: Normative values for the general population. *JBJS* 2002;84:208-215.

Katz J, Losina E, Barret J, et al: The association between hospital and surgeon procedure volume and outcomes of total hip replacement in the United States Medicare population: Health policy implications. *JBJS* 2001;83:1622-1629.

Swiontkowski MF, Buckwalter JA, Keller RB, Haralson R: Symposium: The outcomes movement in orthopaedic surgery: Where we are and where we should go. *JBJS* 1999;81-A:732-740.

V. PANEL MEMBERS

Chair:	Marc Swiontkowski, MD	University of Minnesota	Minneapolis, MN
	Peter Amadio, MD	Mayo Clinic	Rochester, MN
	Michael Goldberg, MD	New England Medical Center	Boston, MA
	Robert Keller, MD	Maine Medical Assessment Foundation	Northport, ME
	Hans Kreder, MD	Univ of Toronto Sunnybrook HSC	Toronto, ON, Canada
	James Weinstein, DO	Dartmouth Hitchcock Medical Center	Lebanon, NH
	James Wright, MD	Hospital for Sick Children	Toronto, ON, Canada

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Panel VIII: Aging and Impairment, Bone Structure and Function

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*

Changes in the quality of bone that often occur with aging are a major health concern for all Americans. In both men and women, there is a decrease in bone mass associated with a loss of bone mineral density. This loss occurs earlier in women and at a faster rate than is seen in men, due in part to differences in peak bone density as well as differences in hormonal regulation and reduction in systemic estrogen subsequent to menopause. As a result, bone is more susceptible to fracture. Loss of bone mineral density is also accompanied by specific loss of the transverse septum linking bone trabecular in the hip and vertebral bodies, leading to compression fractures, pain, disfigurement, reduced mobility, and in some cases, death. While there have been many advances in the pharmacologic prevention and treatment of loss associated with osteoporosis, none of these methods has been shown to restore the normal architecture of trabecular bone. For this reason, the biomechanical properties of the bone remain suboptimal. Aging is also associated with reduced numbers of osteoprogenitor cells needed to repair bone following trauma, further complicating the treatment of musculoskeletal injuries in this population of individuals. Many elderly patients take drugs that may cause osteopenia or reduce the ability of osteoblasts to form bone, further complicating treatment of musculoskeletal injuries. Even in young patients, impairment and/or various drug treatments, can lead to osteopenia or retard bone healing.

B. *Importance to Public Health*

Advances in drug development have benefited health care delivery but many of these treatments have had consequences for bone physiology. Changes in bone and mineral metabolism result in altered bone remodeling and bone quality, modifying the susceptibility to fracture. Trauma involving the musculoskeletal system is also a major health concern in the United States. As the population demographics continue to shift toward a greater number of people older than age 65 years, it is increasingly important to understand how aging affects bone structure and function, how bone structure and function are modified by drugs used to treat aging-related diseases, and how these drugs modify the ability of bone regeneration and repair following injury.

II. RECENT ADVANCES

A. *Bone cell biology*

The past ten years have seen major advances in the understanding of bone cell biology. The mechanisms that regulate osteoclast formation, including those that control the transitions between lineage states from monocytic precursors to pre-osteoclasts and osteoclasts, are being elucidated, permitting development of drugs that target specific states in osteoclastogenesis. Similar advances in mapping the lineage states of osteoblasts have been made. Markers that identify osteoprogenitor cells in the general pool of connective tissue progenitor cells have been found. Research focused on osteocyte biology followed the development of osteocyte cell lines that can be used for cell culture studies. The interrelationships between osteoclasts, osteocytes, and osteoblasts that control bone remodeling have been described including the characterization of factors produced by osteoblasts that regulate osteoclast formation (osteoprotegerin, RANKL) and osteoclast activity (TGF-β), factors that regulate osteoblast formation (cbfa1 and osterix), and factors produced by osteoclasts that modulate osteoblasts (osteopontin, IL-1). Because osteoporosis and other metabolic bone diseases are due to an imbalance in the relationship between bone forming and resorbing cells, this area of investigation is very significant.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

B. *Regulation of cell death*
The understanding of the role of programmed cell death (apoptosis) in the remodeling of musculoskeletal tissues has advanced considerably. The basic mechanisms of apoptosis as they relate to bone cells (osteoblasts, osteoclasts, osteocytes, chondrocytes) have been studied. These studies have shown how regulation of apoptosis affects bone development and remodeling and how it is involved in age-related bone loss and osteoporosis.

C. *Stem cells*
Methods for identifying and isolating mesenchymal stem cells (MSCs), which are multi-potent connective tissue progenitor cells, have been developed, including characterization of surface antigens that are expressed by pre-osteoblasts. This has enabled the development of MSC technology for clinical use in orthopaedics to try to stimulate bone and cartilage formation. New methods have been developed for use of marrow stromal cells in tissue engineering, based on the enrichment of MSCs in the marrow stroma. Such studies have shown that the number of MSCs decreases in aging.

D. *Developmental biology*
Rapid increases in our understanding of how progenitor cells form bone have accompanied advances in developmental biology, especially the development of genetically modified mice. Both naturally occurring mutants and various animal models (knock-outs, knock-ins, and transgenics) have provided outstanding opportunities to determine the roles of specific intracellular and extracellular matrix proteins in the process of bone development and repair, to simulate human bone diseases, and to determine the roles of specific proteins in bone development and disease.

E. *Cell signaling*
Cellular and molecular biology have provided new tools for studying how hormones and other regulatory factors mediate their effects on cell behavior. New signaling pathways have been discovered and characterized. The fact that steroid hormones also use membrane-mediated signaling to exert their effects on cells has been an important advance in understanding how they modulate cell activity. During the past five years, there has been increased understanding of how membrane receptors function. The greatest advances have been in the understanding of how activation of membrane receptors can lead to control of gene expression, providing insight into the cross talk between different membrane receptors as well as with steroid hormone receptors in the nucleus. The idea of mechanotransduction has gained acceptance and efforts to identify and characterize mechanoreceptors in bone cells has increased.

F. *Growth factors*:
The mechanisms by which bone morphogenetic proteins (BMPs) exert their effects on cells have been elucidated. The TGF-β family of growth factors, of which the BMPs are members, has been found to have a variety of effects on bone modeling and remodeling. How these proteins are synthesized, stored, and activated has been a major area of discovery. This information has been used to develop novel therapeutics for treatment of musculoskeletal defects.

G. *Biomineralization*
Advances in imaging bone mineral and its relationship to the extracellular matrix have increased our understanding of how aging and drug treatments modify the structure and function of bone and its material and mechanical properties. During aging the mineral content associated with peak bone mass is reduced, and the distribution of crystal sizes narrows. Some of the therapies used to treat metabolic bone disease have been shown to affect both mineral content and crystal size distribution, while others affect one or the other. The significance of the changes in bone mineral properties for mechanical functions of bone is still being determined. The mechanisms involved in biological mineral deposition are being elucidated. Functions of several individual extracellular matrix proteins have been determined, but the ways in which they act together are still unknown.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

H. *Sex-dependent differences in bone biology*

Both males and females have an age dependent increase in osteopenia and fracture risk, while the mortality and morbidity associated with male osteoporosis are greater. Estrogens and androgens affect male and female cells through different mechanisms. Recent studies have shown that some of the rapid responses to estrogen noted in musculoskeletal cells and present only in cells from females. Androgens do not elicit similar effects in female cells or in male cells. These new observations provide insight into the underlying biological differences that are mechanistically independent of circulating hormone levels, but may be affected by them.

III. FUTURE DIRECTION OF RESEARCH

A. *Cell biology*

1. Determine age-dependent variations in the way cells respond to load, hormones, and cytokines.
2. Identify the intracellular factors that regulate chondrocyte, osteoblast, osteocyte, and osteoclast formation and turnover.
3. Determine how bone and cartilage injury alter the function of their respective cells.

B. *Stem cells*

1. Determine the factors that regulate the differentiation of bone and cartilage forming cells.
2. Evaluate the applicability of stem cell technology to musculoskeletal injury and repair.

C. *Cell Signaling*

1. Mechanotransduction
2. Role of apoptosis in cell signaling for remodeling
3. Neuropeptides and neuropeptides in signaling for remodeling
4. Determine the mechanisms involved in signaling by membrane-mediated
5. receptors for steroid hormones

D. *Architectural factors*

1. Role of cortical bone in fracture prevention in hip and spine
2. Pharmaceutical agents that selectively target cells on periosteal surfaces
3. Role of collagen and collagen defects in mechanical properties, signal transduction and fracture

E. *Bone quality factors in fracture*

1. Mineralization, normal and response to therapeutic treatments
2. Role of bone turnover rate (either increased or decreased) in fracture risk

F. *Growth factors*

1. Understand the mechanisms by which growth factors act at the cellular and molecular levels, and in tissue engineering applications

G. *New biomaterials for reconstruction/tissue engineering*

1. Identify new materials for tissue and organ replacement
2. Understand how materials direct cell behavior

H. *Anabolic therapies for bone and cartilage formation especially for aging tissues*

1. Determine effects of aging on bone and cartilage cell biology
2. Develop new strategies for increasing bone and cartilage in aging populations
3. Study adult stem cell biology with respect to hard and soft skeletal tissues

I. *Gene therapy*

1. Develop new methods for introducing genes in a cell-specific manner
2. Examine the bioavailability of growth factors produced by gene therapy techniques

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

J. *Response to physical factors*
   1. Develop model systems for studying how bone cells respond to physical factors
   2. Examine the mechanisms by which physical factors cause their effects
   3. Identify which cells respond to physical factors
   4. Develop methods for targeted therapeutic use of biophysical factors
   5. Determine how physical factors differ in their regulation of bone and cartilage cells (mechanical stress, shear stress, electromagnetic forces, etc.)

K. *Biomineralization and biomechanics*
   1. Identify predictive models for determining fracture risk.
   2. Determine gene and matrix factors that affect biomineralization and improve mechanical strength.

IV. REFERENCES

Boskey AL: Bone Mineralization, in: *Bone Biomechanics*, ed 3, S.C. Cowen, editor, CRC Press, Boca Raton, FL, 5.1-5.34, 2001.

Boskey, AL: Orthopaedic Surgery: Invited manuscript in: Opportunities for Medical Science in the 21st Century, *JAMA*, 285:619-623, 2001.

Gokhale J, Robey PG, Boskey AL, (eds): The Biochemistry of Bone. In *Osteoporosis*, ed 2, San Diego, CA, Academic Press, Robert Marcus, David Feldman and Jennifer Kelsey, **(eds)** vol 1, 107-189, 2001.

Mendelsohn R, Paschalis EP, Boskey AL: Infrared Spectroscopy, Microscopy, and Microscopic Imaging of Mineralizing Tissues. Spectra-Structure Correlations from Human Iliac Crest Biopsies. *J Biomed Optics* 1999 4**:**14-21.

V. PANEL MEMBERS

Chair:	Barbara D. Boyan, PhD	Georgia Institute of Technology	Atlanta, GA
	Adele Boskey, PhD	Hospital for Special Surgery	New York, NY
	Scott Bruder, MD, PhD	DePuy, Incorporated	Raynham, MA
	David Burr, PhD	Indiana Univ School of Medicine	Indianapolis, IN
	Gloria Gronowicz, PhD	Univ of Connecticut Health Center	Farmington, CT
	Joe Lane, MD	Hospital for Special Surgery	New York, NY
	Nancy Lane, MD	Univ of California, San Francisco	San Francisco, CA
	Clark M. Stanford, MD	University of Iowa	Iowa City, IA

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Panel IX: Health Policy Research

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
We must further our understanding of musculoskeletal health, know the results of our treatment for muscular-skeletal afflictions and finally, how best to deliver this information to the medical community and the public. Accomplishing these goals can be achieved first by obtaining evidence-based data through research activities that address these issues affecting the burden of skeletal-skeletal disease in the population. Utilizing these results, directions can be set through meaningful interaction with policy makers in the government, private sector, and the medical community.

B. *Importance to Public Health*
Defining and articulating the skeletal-skeletal burden of disease and its impact upon the public health will serve as a cornerstone for health policy research.

II. RECENT ADVANCES

A. *Medical specialties*
Policy makers from the public and private sector have suggested there are too many specialties per patient population. The AAOS contracted with the Rand Corporation to examine this issue addressing its validity in the current orthopaedic workforce as compared to the future aging population. A template is also established for future study.

B. *Area variations in health care utilization*
Variations in the delivery of skeletal-skeletal care have been observed. These variations include not only the volume of surgical procedures in different geographic areas but also a variation in the application of these procedures in different populations and cultural groups. The causes for these variations are subject to ongoing research.

C. *Joint replacement*
Joint replacement procedures have been one of the most significant advances in musculoskeletal surgical treatment over the past 30 years. The efficacy and effectiveness of these procedures have been proven after analyzing improvements in quality of life and their cost effectiveness. There is evidence that arthroplasty is an underutilized service in some geographic areas and among some ethnic groups.

D. *Aging and hip fractures*
As our population ages, projections for the number of hip fractures can approach epidemic proportions. Improving the care of hip fractures in our senior population is a major area of concern and one that needs attention. Steps to address these problems have been initiated and are ongoing.

E. *Outcomes instruments*
Outcome instruments have been developed by orthopaedic subspecialty groups. These validated data-gathering tools serve as a basis for obtaining outcome information in areas of: *upper extremity, lower extremity, pediatrics, and spine etc..*

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

F. *Patient safety*
Improved patient safety by eliminating medical errors is identified by policy makers as an area needing immediate attention. Wrong site surgery is such a medical error that also impacts the medical malpractice area. The AAOS has introduced a program to eliminate wrong site surgery. Continued emphasis, however, is needed to make "Sign Your Site" a universally accepted method.

G. *Decreasing orthopaedic risk*
Improving patient safety is achieved by strategies to decrease orthopaedic risk. The analysis of closed claim medical malpractice cases yield important information for decreasing risk.

III. FUTURE DIRECTION OF RESEARCH

A. *Musculoskeletal Awareness*: A top priority should be defining the burden of musculoskeletal diseases and creating public awareness of the costs of these conditions.

B. *Work Force*
1. Maintain an accurate data base and continually update the institution's knowledge and expertise related to the musculoskeletal physician workforce (survey research to include in particular the short- and long-term effects on the scope of practice of the younger members).
2. How to address and improve diversity in orthopaedic training and manpower?
3. Projections of future need?

C. *Orthopaedic Practice Management*
1. Develop best practices studying business models and/or specific musculoskeletal problems (e.g. pediatric problems, trauma care, etc) in order to deliver cost effective care.
2. Research upon issues relating to Medicare payment policy (e.g. practice costs, malpractice costs and physician work) in order to empower musculoskeletal specialists to engage in meaningful dialogue with policymakers.
3. Develop programs to improve the patient-physician relationship and communication regarding patient care and musculoskeletal health.

D. *Delivery of Orthopedic Care*
1. Develop outcomes data to assess the impact on quality of life and cost-effective treatments.
2. Identify the methods of obtaining outcomes data in the clinical office setting addressing the time, workforce, and cost involved in gathering this data.
3. What are the barriers to domestic volunteerism among orthopaedic surgeons and how can they be removed? Is orthopaedic volunteerism effective in improving the delivery of musculoskeletal care to underserved areas in the U.S.?

E. *Patient Safety*
1. Develop appropriate workable definition and interpretation of "medical error". Is the following correct: "a preventable or potentially preventable, adverse or potentially adverse (no matter how trivial) event"?
2. How to reduce medical errors by studying "near misses" in orthopaedic practice. Once identified, determine ways to best effect change. ("Near misses" refer to occurrences that do not actually lead to an untoward event but could eventually result in an error that causes harm if permitted to occur repeatedly.)
3. Explore geographic variations in musculoskeletal malpractice claims.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

F. *Physician Education*
   1. Refine the educational effectiveness of motor skills testing and virtual reality operating experiences as a measure of competence.
   2. Does current residency curriculum and testing (driven by the AAOS Orthopaedic Knowledge Update) translate into competence?
   3. Can changes be made in the medical school and resident training curriculum for MD/DO providers of musculoskeletal care (i.e. introducing data on managing malpractice risk) and how would such changes alter the delivery of care?

G. *Public Health*
   1. Study the physiologic effects of a routine exercise program (walking, running, swimming, weight training) and its impact upon the frequency and severity of musculoskeletal conditions (i.e. back pain).
   2. Study reducing the impact of musculoskeletal disabilities by evaluating the effect of excess weight.
   3. Effect upon skeletal-skeletal health of having widespread utilization of a readily available and affordable (covered benefit) bone density test.
   4. Patient Outcomes vs. Surgeon Volume.
   5. What are the processes and attributes of high-volume hospitals and high-volume surgeons (>50/year) for having fewer complications than low-volume hospitals and surgeons in total hip replacement?
   6. Study the relationship between quality and volume in total joint arthroplasty.

H. *Improving Hip Fracture Care*
   1. Research recommendations from National Consensus Conference On Improving The Continuum Of Care For Patients With Hip Fracture.
      a. Therapeutic exercise interventions to prevent falls.
      b. Pharmacologic management of osteoporosis.
      c. Development of hip protectors to prevent the fracture when falls do occur.
      d. Develop appropriate cost-effective methods to evaluate causes of secondary osteoporosis at the time of the hip fracture.
   2. Identify essential services needed to optimize the outcomes, particularly in the context of the heterogeneous hip fracture population.
   3. Identify the parameters to be used to determine appropriate length of stay in the acute and rehabilitative settings.
   4. Develop criteria to determine transfer to acute or sub-acute rehabilitation centers, skilled nursing facility or discharge to home. These criteria should include milestones that determine when utilization of these alternate care settings have been optimized and no further benefits can be anticipated.

IV. SELECTED REFERENCES

Brennan, TA et al: Results of Harvard Medial Practice Study I. *NEJM* 1991;324:370-376.

Dartmouth Atlas of Musculoskeletal Health Care. AAOS. 2000.

Drewett RF, Minns RJ, Sibly TF: Measuring outcome of total knee replacement using quality of life indices. *Ann R Coll Surg Engl*. 1992 Jul;74(4):286-9; discussion 289-90.

Patient Outcomes After Knee Replacement: D.A. Heck, R. Robinson, C.M. Partridge, R. Lubitz, and D.A. Freund. *CO Rel Res* 356:93-110, 1998.

Heckman JD, Lee PP, Jackson CA, et. al.: Orthopaedic workforce in the next millennium. *J Bone Joint Surg Am* 1998 Oct;80(10):1533-51.

Hirsch HS: Total joint replacement: a cost-effective procedure for the 1990s. *Med Health R I*. 1998 May;81(5):162-4.

Katz JN, et al: Association between Hospital and Surgeon Procedure Volume and Outcomes of Total Hip Replacement in the US Medicare Population. *JBJS Am* 2001; 83:1622-29.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Kohn LT, Corrigan JM, Donaldson MS (Eds): To Err is Human: Building a Safer Health System. Institute of Medicine, National Academy Press, 2000.

Leape, LL et al, Results of Harvard Medial Practice Study II. *NEJM* 324:377-384. 1991

Managing Orthopaedic Malpractice Risk—2nd Edition. AAOS. 2000.

Morris, AH; Zuckerman JD: National Consensus Conference on Improving the Continuum of Care for Patients with Hip Fracture. *JBJS* April 2002.

Norton EC, Garfinkel SA, McQuay LJ, Heck DA, Wright JG, Dittus R and Lubitz RM: The Effect of Hospital Volume on the In-Hospital Complication Rate in Knee Replacement Patients: *HSR* 33(5):1191-1210, 1998.

Norwold, DL: Measuring Competency. *Bulletin of the American College of Surgeons*. Vol 85(11).

Rissanen P, Aro S, Sintonen H, et. al.: Costs and cost-effectiveness in hip and knee replacements. A prospective study. *Int J Technol Assess Health Care*. 1997 Fall;13(4):575-88.

Wrong Site Surgery: AAOS Advisory Statement. 1997, revised 2002. Prepared by Alan H. Morris MD.

V. PANEL MEMBERS

Chair:	Alan Morris, MD		Clayton, MO
	Douglas Jackson, MD		Long Beach, CA
	Bob Fine, JD	AAOS, Dept. of Socioeconomic and State Society Affairs	Rosemont, IL
	William Healy, MD	Lahey Clinic	Burlington, MA
	James D. Heckman, MD	Journal of Bone and Joint Surgery	Needham, MA
	William Herndon, MD	Oklahoma Sports Science and Orthopaedics	Edmond, OK
	David Lovett, JD	AAOS, Washington Office	Washington DC
	David Wong, MD	Denver Orthopaedic Clinic, PC	Denver, CO
	Joseph Zuckerman, MD	New York University	New York, NY
Comments by:	Jack Childers, MD		Lutherville, MD
	Richard Haynes, MD	Shriner's Hospital	Houston, TX
	Robert Haralson, MD	Southeastern Orthopaedics	Knoxville, TN
	William Robb, MD	Northwestern University	Chicago, IL
	Gilbert Shapiro, MD		New Bedford, MA
	Edward Toriello, MD	Wyckoff Heights Medical Center	Middle Village, NY

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Panel X: Gender and Sex Issues

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*

"Musculoskeletal medicine is one of the areas in which appreciation of the effects of sex and gender most influences treatment and outcome."[1] With the recognition of not only differences in disease prevalence and type between men and women, but of differences at the cellular and biological levels as well, investigating differences in musculoskeletal system growth, repair, and interactions with other systems are necessary.[4] As women are the most frequent consumers of musculoskeletal medicine, the particular features of their musculoskeletal health and their disease outcomes call for further research.

Arthritis, which encompasses more than 100 diseases, is the most prevalent chronic condition in women. [2,3] Osteoarthritis, which is three to four times more common in women than in men, is a leading cause of disability and functional limitations.[2,3] The prevalence of osteoporosis is also much greater; more than 80% of patients affected are women.[1] Female participation in sports and exercise continues to expand; this expansion has highlighted increased rates of musculoskeletal injury among women compared to men.[5] Differing responses to physical training and physiology are hypothesized as the underlying causes and the types of increased injury in women, but much more study is needed.[5] Women respond differently to anesthesia, and pain medication than men, hence an understanding of the mechanism of these differences will be crucial in both selection of appropriate anesthesia during operative procedures and for management of the above conditions (Lugato ref, Adam's Rib).

B. *Importance to Public Health*

Women bear a disproportionately larger burden of musculoskeletal disease and disability than do men.[1] This fact, combined with a US female population that is increasingly larger, older, and more active, necessitates a more intense focus on women's musculoskeletal health.

II. RECENT ADVANCES

A. *Female Knee Injury Mechanisms*

Mechanisms for higher rate of knee injury in the female athlete have been postulated.

B. *Estrogen Healing Properties*

Mechanisms of estrogen's action on ligament healing and bone cell metabolism have been described.

C. *Cell Biology*

Demonstration that cells from females and males respond differently to therapeutics, growth factors, and cytokines.

D. *Bone Fragility*

1. Differences in peak bone mass and fracture risk in men and women have been linked to specific genes.
2. Large clinical trials of anti-resorptive agents using fracture as an endpoint have been completed.

E. *Cancer*

Advances in our understanding of why prostate and breast cancer cells preferentially metastasize to bone.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

F. *Osteoarthritis*

Description of sex specific markers predictive of early osteoarthritis.

III. FUTURE DIRECTION OF RESEARCH

A. *Basic Science*

1. Investigate the sex-specific molecular signals that control repair and growth in cells of the musculoskeletal system.
2. Determine whether there are sex-specific differences in muscle, soft tissue, and bone damage.
3. Expand our understanding of the influence of sex on development of autoimmune disorders.
4. Explore the interaction of the immune, vascular, and musculoskeletal systems in women.
5. Determine if there are sex-specific differences in immune acceptance of allografts, xenografts, and synthetic biomaterials.
6. Develop synthetic and tissue engineering replacements for muscle, soft tissue, and bone that are optimized for use in women.
7. Determine the molecular basis for the sexual differences in response to anesthesia and pain medication.

B. *Arthritis*

1. Investigate why there is a greater prevalence of arthritis in women than in men.
2. Explore the biological and mechanical factors that trigger the development and progression of arthritis.
3. Investigate how the biological repair processes and bioengineering approaches to tissue regeneration, replacement, and repair in men and women might be different.
4. Develop sex-specific markers for osteoarthritis and rheumatoid arthritis.
5. Develop sex-specific animal models for the study of the molecular mechanisms of osteoarthritis and rheumatoid arthritis.

C. *Osteoporosis*

1. Explore the sex-specific factors that contribute to the development of peak bone mass.
2. Develop additional biologic markers for early detection of bone loss.
3. Develop genetic markers for detecting persons at risk for bone loss.
4. Develop and enhance imaging technologies that enable the early detection of bone loss.
5. Develop strategies which will optimize the maintenance of bone mass throughout life.
6. Develop strategies for improving the quality of life in women with osteoporotic fractures.
7. Explore the role of physical activity in preserving muscle strength, balance, and coordination as a means of enhancing bone quality and preventing falls in the elderly.
8. Develop agents that will stimulate bone formation and maintain bone quality.

D. *Physical Activity and Sports Medicine*

1. Improve gender specific research instruments for assessing energy expenditure.
2. Determine the type, intensity, duration, and frequency of physical activity that is important for musculoskeletal health in women.
3. Develop strategies to prevent and investigate the biologic mechanisms that contribute to the “female athlete triad”
4. Investigate the role of physical activity in the development of bone, tendon, ligament, and muscle.
5. Determine why gender differences exist in the prevalence and etiology of stress fractures and other overuse syndromes and develop strategies for prevention.
6. Determine how sex-based influences in osseous anatomy, ligamentous laxity, and sex hormones influence the development of musculoskeletal disorders

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

E. *Clinical Considerations*

1. Investigate the role of women's footwear in the development of deformity, pain, disability and falls
2. Explore how gender and cultural variations influence access to musculoskeletal care
3. Explore how gender and cultural variations influence treatment outcomes

IV. REFERENCES

[1]Tosi, L. L. (2000). Women and the orthopaedic surgeon. Clinical Orthopaedics and Related Research, 372, 17-31.

[2]Centers for Disease Control and Prevention. (1995). Prevalence and impact of arthritis among women-United States, 1989 1991. MMWR Morbidity and Mortality Weekly Report, 44, 329-334.

[3]Callahan, L. F., Rao, J. & Boutaugh, M. (1996). Arthritis and women's health: prevalence, impact, and prevention. American Journal of Preventive Medicine, 12 (5), 401 – 162.

[4]Garrett, W. E., Lester, G. E., McGowan, J. & Kirkendall, D. T. (Eds.). (2001). Women's Health in Sports & Exercise. Rosemont, IL: American Academy of Orthopaedic Surgeons.

[5]Garrett, W. E., Lester, G. E. & Lopiano, D. (2001). Introduction. In W. E. Garrett, G. E. Lester, J. McGowan & D. T. Kirkendall (Eds.), Women's Health in Sports and Exercise (pp. xix – xxiv). Rosemont, IL: American Academy of Orthopaedic Surgeons.

V. PANEL MEMBERS

Chair:	Leigh F. Callahan, PhD	Univ of North Carolina School of Medicine	Chapel Hill, NC
Co-chair:	William Garrett, MD, PhD	Univ of North Carolina School of Medicine	Chapel Hill, NC
	Adele Boskey, PhD	Hospital for Special Surgery	New York, NY
	Barbara Boyan, PhD	Georgia Institute of Technology	Atlanta, GA
	Marc Galloway, MD	Cincinnati Sports Medicine Research and Education Foundation	Cincinnati, OH
	Letha Griffin, MD	Peachtree Orthopaedic Clinic	Atlanta, GA
	Jo Hannafin, MD	Hospital for Special Surgery	New York, NY
	Joe Lane, MD	Hospital for Special Surgery	New York, NY
	Laura Tosi, MD	Children's Hospital	Washington DC

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel XI: Spinal Problems

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Clinically important spinal disorders fall into two categories, painful spinal disorders and deformities.

Back and neck pain are extremely common. It's estimated that 85% of people have a back pain at some time in life. At any given moment, 10% to 15% of the adult U.S. population experience low back pain. Back pain is the most frequent cause of activity limitations in people younger than 45 years of age, the second most frequent reasons for physician visits, and the third ranking reason for surgical procedures. About 11% of Americans report low back impairment or reduced ability to function. Every year, 2% of the employed population lose time from work because of back pain. Half of these are receiving compensation for lost wages.

Spinal deformities, while less common cause not only pain, but also may influence the function of other organ systems. Further, deformities are often the cause of pain as well as being cosmetically important. Structural deformities related to scoliosis and other spinal disorders in children can be a serious burden to these otherwise healthy individuals.

B. *Importance to Public Health*
Back pain, and in particular, low back pain, affects one in four persons in the United States in any one year. In 1998, national health statistics reported 16.4 million physician visits and/or hospitalizations for back conditions, with nearly 24 million persons reporting back pain on most days for at least one month during the year.

II. RECENT ADVANCES

A. *Magnetic Resonance Imaging*
The diagnosis of many spinal conditions, particularly those related to degenerative and/or structural changes, has improved dramatically with the introduction and availability of magnetic resonance imaging (MRI). Unfortunately, the relationship of many degenerative and or structural changes to pain and other symptoms, often are uncertain. Many observed "abnormalities" are part of the normal aging process and others are coincidental to the patient's symptoms.

B. *New Surgical Techniques*
The treatment of degenerative disc disorders including related spinal problems such as disc herniation, spinal stenosis, and degenerative spondylolisthesis has improved as new surgical techniques have been introduced and non-operative treatments have been better evaluated. Even so, treatment remains unsatisfactory for a large number of patients and surgical indications and choices remain controversial.

C. *Understanding of Degenerative and Aging Processes*
The understanding of the pathophysiology of the degenerative and aging processes has improved significantly. Both biological and biomechanical aspects have been better clarified, leading to optimism regarding prevention and treatment. For example, the use of growth factors has been found to stimulate disc cells in vitro and in animals.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

D. *Understanding of Pain*
Improved understanding of pain, its sources, pathways, and developments provide promising building blocks for effective treatment and modification of chronic pain.

III FUTURE DIRECTIONS OF RESEARCH

A. *Diagnosis*
1. Presently our best diagnostic tool for identifying disc degeneration is the MRI scan. Although its sensitivity and specificity in that context are quite high, its ability to localize the source of pain is poor.
2. Other techniques to localize the pain source such as provocative discography remain controversial because of poor sensitivity and specificity.
3. There is no acceptable method available to determine if “minor” instability of a motion segment exists. Gross instability can be identified using flexion-extension or similar provocative radiographic techniques. The resolution can be improved by implantation of markers, an impractical method for clinical use.
4. Methods to determine the role of muscles and connective tissue and back pain are poor. Measurements of consequences of back pain such as strength, endurance, and coordination are not universally accepted.
5. There is no accepted method to functionally evaluate a patient with back pain. Because pain is a major symptom of many musculoskeletal conditions, development of common definitions, measurement, quantification and means of evaluating pain should be a high priority.

B. *Randomized, controlled trials for surgical and non-surgical treatment of back disorders.*
There are a variety of spinal disorders such as herniated lumbar discs, spinal stenosis, spondylolisthesis, and degenerative disc disease that are common but where treatment and outcome are not well established. Treatment should ideally be based on results from prospective randomized control trials. Without this information, controversy over the treatment of these common conditions will continue with immense medical and socio-economic repercussions.

C. *Acute and Longer Term Complications from Surgical Treatment*
As anesthetic and perioperative medical management capabilities continue to improve, larger and larger spine surgeries are being performed in older and sicker individuals with severe spine problems. Additional studies are warranted on the systemic complication of spine surgery in both the young and older populations. Complications that deserve special merit include vascular complications following anterior lumbar surgery, bone graft donor site morbidity, nonunion with various types of graft material, the impact of cigarette smoking, corticosteroids, nonsteroidal anti-inflammatory drugs and chemotherapeutic agents on bone healing, difficulty swallowing and speaking following anterior cervical surgery, and incision pain following thoracotomy versus less invasive thorascopy.

D. *Treatment of Degenerative Disc Disease*
1. Development and evaluation of artificial intervertebral disc and nucleus. The prosthetic approach preserves motion. Existing European outcomes appear excessively “optimistic.” Presently, clinical trials in the U.S. are underway that should be supported.
2. Growth factors have been shown to stimulate matrix production in vitro and in animals. The introduction of growth factors or transporting genes into the nucleus that activate matrix synthesis or prevent matrix breakdown need development and evaluation.
3. The development of chondrocyte technologies to facilitate annular repair.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

E. *Emerging Technologies*
Emerging technologies in spine care include intradiscal treatment using heat-generating devices. These treatments aim primarily at the painful degenerative disc. The basic science underlining the procedures remains unclear. Other emergent technology includes vertebroplasty and kyphoplasty. In both of these procedures, vertebral fractures are treated by injection of bone cement. In kyphoplasty, a balloon is first inserted, aimed at obtaining deduction and providing a cavity for the cement. Replacement of the nucleus pulposus, so- called nucleoplasty of the entire disc, and so-called disc replacement, are other emerging technologies. These procedures also address the painful intervertebral disc. While early results are encouraging, all these emerging technologies should be further tested in randomized controlled trials, and their long-term results remain uncertain at present time.

F. *Treatment of Chronic Back and Neck Pain*
Chronic pain, not only as it applies to the painful spine, requires a different approach than acute pain. Current treatment alternatives range from medication to implantable stimulators and behavioral modification. All of these treatment alternative require further study and none has been found to be singularly effective in large groups of patients.

G. *Spinal Deformities*
The cause of idiopathic scoliosis remains unclear. A variety of contributing factors have been explored, but the cause remains elusive. At the present time, it is also unclear which curves will progress and which will not. Screening programs and treatment alternatives should be further studied.

H. *Basic Science: Biology*
1. The Biological Basis for Fusion Enhancement: It is now apparent that use of BMPs will facilitate biologic enhancement of spine fusions. While this is an exciting development, several important questions remain unanswered. 1) Do all BMPs work equally well? 2) What is the optimum resorption time and composition of the carrier/scaffold to deliver the BMP? 3) Are there better strategies for BMP delivery such as time-released, gene therapy, cell-medicated? 4) Will the cost justify the clinical outcomes in all situations or only in compromised hosts or failed fusions? 5) Will internal fixation be needed in routine degenerative fusions or only in deformity and trauma/instability?
2. Biological Treatment of Degenerative Disc Disease: The chondrocyte-like disc cells in annulus fibrosis (AF) and nucleus pulposus (NP) produce matrices under the control of a variety of substances including growth factors. Catabolic process or breakdown of the matrix is mediated by various matrix metalloproteinases (MMPs) and cytokines. There is balance between the anabolic and catabolic processes in the normal disc, but this balance is lost in degenerating discs. The intervertebral disc also requires nutrition, mainly by diffusion form the vertebral bodies and endplates. Biological repair or regeneration may become feasible for injecting a growth factor or bone morphogenetic proteins (BMPs) or transplanting cells that are transfected with therapeutic DNAs by viral or non-viral gene therapy. Molecular biology also will help identify candidate genes responsible for disc degeneration and repair. Tissue engineering of the intervertebral disc may restore disc tissues biologically rather than surgery. Biological treatment for DDD is in the early research phase, but if it becomes successful, many patients with chronic pain associated with DDD will be helped by simpler and less invasive treatment.

I. *Biomechanics*
1. Biomechanics of Spinal Degeneration: Human disc, ligaments, and the facets work in unison to transmit loads and motions across a motion segment or functional spinal unit (FSU). The FSU consists of two adjacent vertebrae and the interconnecting ligaments and disc. For this reason, if the degenerative process affects one

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

component others follow. In general, degenerative changes result in decreased disc heights, increased ligament laxity, and decreased ROM. Recent efforts are underway to restore disc function by replacing the disc with a “mechanical” disc and restoring the collapsed osteoporotic vertebral bodies with cement. It is important that the interaction between biomechanics and biology be pursued at the cellular level to gain further understanding of the role of mechanical factors in producing degeneration, in preventing/slowing down the degeneration, and/or replacing a degenerated spinal element.

2. Biomechanics of Motion Segment and Clinical Instability: FSU mechanical properties vary with spinal level and motion direction, mostly because of the varying vertebral size, facet orientation, and disc geometry. Modern imaging techniques, such as MRI, may enable us to study the in situ response of FSU in patients with various spinal disorders, including spinal instability. New technological advances in the area of micro- and nano-scare sensors may afford a unique pathway to determine in situ loads in subjects during activities of daily living.

J. *Neurobiology/Pain Research*

In acute and subacute pain, the nociceptors are sensitized by chemicals released from the immune system, vascular system, nerve endings, and injured tissue. These chemicals include bradykinins, prostaglandins, histamine, substance P, and cytokines. These chemicals either sensitize or activate nociceptors. Cytokine inhibitors and membrane channel blockers that act on specific sites in the peripheral and central nervous system may be useful in alleviating musculoskeletal pain in the future.

IV. SELECTED REFERENCES

National Center for Health Statistics, National Ambulatory Medical Care Survey (NAMCS). 1998.
National Center for Health Statistics, National Hospital Discharge Survey (NHDS). 1998.
National Center for Health Statistics, National Health and Nutrition Examination Survey (NHANES). 1988-1994.
Praemer A, Furner S, Rice DP. Musculoskeletal Conditions in the United States. 1999: 27.
Weinstein SL, Dolan LA, Spratt KF, Peterson KK, Spoonamore MJ, Ponseti IV. Health and function of patients with untreated idiopathic scoliosis: a 50-year natural history study. JAMA 2003 Feb 5;289(5):559-67.

V. PANEL MEMBERS

Chair:	Gunnar B. J. Andersson, MD, PhD	Rush Presbyterian St. Lukes Med Ctr.	Chicago, IL
Co-chair:	Edward Hanley, MD	Carolinas Medical Center	Charlotte, NC
	Howard An, MD	Rush Presbyterian St. Lukes Med Ctr.	Chicago, IL
	Scott Boden, MD	Emory University	Decatur, GA
	John Cavanaugh, MD	Hospital for Special Surgery	New York, NY
	Sanford Emery, MD	Univ Hospitals of Cleveland	Cleveland, OH
	Steven R. Garfin, MD	Univ of California, San Diego	San Diego, CA
	Vijay K. Goel, PhD	University of Iowa	Iowa City, IA
	Thomas R. Haher, MD	St. Vincent Catholic Medical Center	New York, NY
	Harry N. Herkowitz, MD	Beaumont Hospitals	Royal Oak, MI
	Serena S. Hu, MD	Univ of California, San Francisco	San Francisco, CA
	Manohar Panjabi, MD, PhD	Yale Medical School	New Haven, CT

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Panel XII: Neoplasia

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*

Evaluation and management of tumors of the musculoskeletal system are of great clinical significance in the field of orthopaedics. Orthopaedic surgeons continue to have a leading, if not primary, role in the treatment of primary bone and soft tissue sarcomas and an important contributory role in the management of metastatic bone disease. Over the past two decades considerable advances have been made in the treatment of musculoskeletal neoplasms. Patient survival has been improved with more effective chemotherapeutic and surgical treatments. The role and methods of adjuvant radiotherapy has been better defined. Improved techniques of surgical resection and reconstruction have made limb salvage procedures commonplace and with better functional outcomes. Considerable challenges remain, however, with many current research efforts focused on these issues. Specific topic areas of recent advances include investigations into the genetics of sarcoma and expression of the multi-drug resistant gene; improvement in limb salvage reconstructive techniques for both bone and soft tissue sarcomas; issues related to safety and preservation of allograft tissues and insight into the mechanisms of metastatic disease dissemination, prevention of bone metastases and optimal techniques of skeletal restoration in patients with actual and impending pathologic fractures.

B. *Importance to Public Health*

Cancer remains a leading public health concern in the United States. It is estimated that in 2002, nearly 1.3 million new cases of cancer will be diagnosed and 555,500 people will die from cancer in the United States. Bone is the most frequent site of metastatic spread and is particularly common in patients with breast and prostate tumors. The incidence of bone metastases at autopsy ranges from 47% to 85% in patients with breast cancer and from 33% to 85% in those with prostate cancer. Because patients with cancer are living longer, strategies to prevent bone metastases or treat established bone disease are of even greater importance. Moreover, cancer remains the second leading cause of death in children from ages 1 to 14 years, with an estimated 2,400 new cases of bone sarcoma in 2002. Finally, primary soft tissue sarcomas continue to threaten life and limb with an estimated 8,300 new cases in 2002.

Safety issues related to allograft tissues are also a recognized public health concern. The use of musculoskeletal allograft tissue in the United States has dramatically increased from approximately 350,000 tissues used in 1990 to 800,000 in 2000. While disease transmission and infection remains extremely low, recent deaths related to infected allograft tissue has heightened awareness of the need for proper tissue processing procedures and regulation of tissue banks. Since 1998 the FDA has required screening and testing of tissue donors, including testing for HIV and hepatitis.

II. RECENT ADVANCES

A. *Genetics in Sarcoma*

1. *Multi-Drug Resistance*

While the 5-year survival rate of patients with osteosarcoma has dramatically improved from 10% a few decades ago to a current rate of 65%, it is now apparent that 25% to 30% of patients are resistant to current chemotherapeutic agents due to one or another mechanism of multi-drug resistance (MDR). Patients expressing MDR have a problematic outcome; identification of those patients will promote the development of novel treatment strategies. The expression of the multi-drug resistant gene, MDR-1, is a P-glycoprotein

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

(PGP), which is an active transporter of certain compounds out of the cell, including chemotherapeutic agents. Some studies have shown a relation between PGP expression and outcome following multi-drug chemotherapy whereas other studies have not. Percent necrosis remains the current best prognostic indicator for osteosarcoma with the exception of the presence of metastatic disease.

2. *Tumor Specific Translocations*
   Tumor specific translocations in the Ewing's Family of Tumors (EFT): Approximately 85% of the EFT exhibit the balanced t(11,22) translocation which encodes for the fusion transcript EWS/FLI-1. Another 10-15% encode for EWS/ERG fusion product. Three other fusion genes (EWS/ETV1, EWS/FEV, and EWS/E1AF) have been identified in a small number of patients. Controversial data exist as to the prognostic significance of the various subtypes of EFT.

3. *Prognostic markers*
   Recent retrospective analyses have shown a correlation between the expression of the Her-2-Neu oncogene and a poor prognosis. The expression of vascular endothelial growth factor has a similar association. Loss of heterozygosity of the Rb gene has also been shown to portend a worse prognosis. Mutation of the ubiquitous tumor suppressor p53 is probably an early event involved in oncogenesis.

4. *Identification and localization of novel tumor suppressors*
   Early studies have shown multiple regions of loss of heterozygosity in osteosarcoma. Recently two of these regions (chromosome arms 3q and 18q) have been identified and shown to contain potential novel tumor suppressor genes that may play a role in oncogenesis or disease progression.

5. *cDNA micro array technology*
   This technique has rapidly expanded the ability to identify gene expression differences between RNA from different tissues. Recent work has identified multiple differences in expressed sequences between primary and metastatic osteosarcoma in a murine model.

B. *Limb Salvage in Bone Sarcomas*

1. *Processing of allograft bone and tissues:* Presently most large tissue banks are accredited by the American Association of Tissue Banks (AATB) and follow AATB guidelines and regulations regarding the processing and storage of allograft tissues. However, current testing for HIV and hepatitis are imperfect. These screening tests used in tissue processing cannot detect the very early presence of virus. This window period (e.g. the time between infection and the ability of the screening test to detect the virus) is approximately 22 days for HIV, 56 days for HBV and 70 days for HCV.

   In an effort to improve safety with tissue banking, the FDA published regulations in 2001 requiring all tissue banks to register with the FDA. This will result in the first complete listing of all companies involved with tissue banking and allow for monitoring of tissue practice requirements proposed by the FDA. Furthermore, new tissue processing standards were established by the AATB in 2002 requiring all tissue to be cultured prior to exposure of the tissue to antibiotics or sterilizing agents. Specific recommendations included discarding any tissue contaminated with anaerobic spore-forming organisms unless the contaminant can be removed by a validated process.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

2. *Bone allograft reconstruction*

Reconstruction with large segmental bone allografts provide satisfactory function in approximately 70% of patients, depending on the type of graft employed. Concern over transmission of bacterial and viral diseases with large segment allografts has lead to recent scrutiny of tissue banking screening and procurement procedures. Such potential for disease transmission can be reduced by irradiation of the grafts. Unfortunately irradiation also makes the graft more brittle due to the destruction of collagen alpha chains, probably mediated by free radicals generated from water molecules. One recent study hypothesized that freezing, which reduces the mobility of water molecules, may decrease the production of such free radicals and found that allograft irradiated at –78 degrees C was less brittle and had less collagen damage than when irradiated at room temperature. While some concerns remain, bone allografts are considered safe with use of the current standards proposed by the American Association of Tissue Banks.

Recent studies of incorporation of allograft into host bone show that such healing may be improved with pre-processing of the allografts. Laser-perforated and partially demineralized allografts show histological evidence of complete incorporation into host bone.

3. *Prosthetic reconstruction*

Modular oncologic prosthetic implants permit good to satisfactory functional restoration in limb salvage and avoid the potential complication of nonunion and fracture associated with large segmental allografts. Recent advances in prosthetic design include expandable implants that can be lengthened with noninvasive means for reconstruction in skeletally immature patients. The main limitation of prosthetic reconstructions, however, has been the inability to achieve effective attachment of host soft tissues to the implant. The development of new materials that permit solid attachment of host soft tissues to the metal implant are now being used in the development of new modular oncology implants.

C. *Tissue Engineering in Orthopaedic Oncology*

1. *Bone graft substitutes*

Though comparative studies are lacking, a number of bone graft substitute materials are now available and in clinical use as bone void fillers. Bone graft substitutes and growth factors are also finding a place in enhancement of bony union, another important need relative to allograft use in oncologic reconstructions.

2. *Engineered musculoskeletal tissue*

Advances have been made in the control of cellular differentiation of mesenchymal cells into specific tissues in vitro.

D. *Multimodality Management of Soft Tissue Sarcomas: Adjuvant chemotherapy*

In the past two decades advances in imaging techniques and radiation therapy have enhanced successful limb salvage in soft tissue sarcomas. Death rate from metastases in patients with high-grade, non-rhabdomyosarcoma soft tissue sarcomas was not impacted, however, and prompted efforts to find effective adjuvant chemotherapy. Although the value of adjuvant chemotherapy is still debated by some, many institutions now utilize preoperative multi-drug chemotherapy in the management of high-grade soft tissue sarcomas with early results suggesting improved survival.

E. *Metastatic Bone Disease*

1. *Mechanisms of Disease Dissemination*

Mechanisms of invasion at the primary site of tumor are being elucidated by the characterization of the role of tumor cells and host-cell-secreted extracellular matrix enzymes that facilitate invasion (e.g. metalloproteinase enzymes). Adhesion of metastatic cells to endothelium and trans-endothelial migration has been investigated. Findings indicate that cell surface integrin molecules and extracellular matrix proteins are involved

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

in this process. Other studies have focused on the roles of angiogenesis and bone resorption in the growth of tumor cells at sites of metastases.

2. *Prevention of Skeletal Metastases*
   It is now established that osteolytic, mixed, and osteoblastic skeletal cancers stimulate significant localized osteoclast-mediated bone resorption. This mechanism of tumor-induced, osteoclast-mediated bone resorption is thought to be operational in metastatic breast cancer, myeloma, prostate cancer, and essentially any cancer that alters the local balance between bone formation and bone resorption. With the knowledge that osteoclasts, the body's principal bone-resorbing cell, play a pivotal and pathologic role in skeletal metastasis, much attention has been focused on clinical trials using bisphosphonates, a family of drugs that influence osteoclasts by decreasing osteoclast number and osteoclastic bone resorption. Well-controlled clinical trials studying breast cancer and myeloma have demonstrated a statistically significant decrease in the number of skeletal complications in patients who have osteolytic cancers treated with bisphosphonate pamidronate.

3. *Operative Treatment of Skeletal Metastases*
   Vertebroplasty, developed for the treatment of osteoporotic spinal compression fractures, has now been effectively used in the treatment of symptomatic spinal metastases in selected patients. Clinical indications for various methods of surgical treatment of actual or impending pathologic fracture continue to be refined. Recent studies show improved results with prosthetic replacement as opposed to osteosynthesis in operative treatment of long bone metastases.

III. FUTURE DIRECTION OF RESEARCH

A. *Genetics in Sarcoma*

1. *Molecular Staging*
   With few new chemotherapeutic agents on the horizon for the treatment of sarcoma patients, large prospective clinical studies should be performed to identify genetic markers (e.g. translocations in EFT and MDR gene in osteosarcoma) and define their prognostic significance. Other potential markers that may have prognostic impacts in treatment of patients with osteosarcoma, such as INK4A, Her-2-Neu and VEG-F should similarly be evaluated. Such combined investigations will require tissue procurement at the time of diagnosis and clinical correlation. If proven, these markers may allow patients at high risk for relapse to be treated with more aggressive or different therapies than patients at lower risk.

2. *Therapeutic targets*
   The EWS/FLI-1 fusion transcript has already been successfully targeted with anti-sense oligonucleotides *in vitro* and *in vivo*. Much work needs to be done to elucidate the molecular mechanisms of oncogenesis and the metastatic process in bone sarcomas. Each step identified in these pathways could be a potential target for intervention

3. *Model development*
   There is a lack of appropriate phenotypic models for human bone sarcomas. The development of both in vitro and in vivo models would greatly facilitate the elucidation of both oncogenic and metastatic mechanisms and provide a means for testing therapeutic interventions.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

4. *Micro-array analysis*
   The field of high throughput gene expression analyses is generating large volumes of data. This information is of great importance. However, the interpretation of this data will be a challenge requiring computer power and techniques in cellular and structural biology and the post-genomic field of proteomics.

B. *Limb Salvage for Bone Sarcomas*
   1. *Processing of bone and allograft tissues*
      Improved safety of allograft tissue is the direction of future research. While the risk of disease transmission is extremely low, research into better techniques of processing and sterilization of allografts are necessary. Furthermore, oversight of all tissue banks is needed to ensure compliance with appropriate standards for tissue handling. Reporting of all adverse episodes by the surgeon to a central data bank would also provide data to promote patient safety. The FDA has engaged in dialogue with industry regarding this. Finally, implementation of new testing which can shorten the window period when viral presence is not detected is being considered for application (e.g. use of the nucleic acid test which would decrease the window period for HIV to 7-12 days, for HBV to 41-50 days and for HCV to 120-29 days).

   2. *Bone Allografts*
      Although the risk of disease transmission is extremely low, research into better techniques of secondary sterilization of allografts (both bone and tissue) are still necessary. Current techniques of cryopreservation limit chondrocyte survival to the superficial layer of the articular cartilage. With improved methods of cryopreservation, longevity of the articular surface of the allograft may improve and promote the use of osteoarticular reconstructions, considered a more biologic reconstruction than an allograft combined with a prosthesis for reconstruction of the articular surface.

      Future investigation of improved fixation methods may decrease the risk of allograft fracture. With recent studies suggesting that devices that create holes in allografts increase the likelihood of fracture, the design and use of devices that do not penetrate the allograft yet provide stable fixation (e.g. plates with cerclage wires or unicortical locking screws) may lead to a reduction in allograft fractures.

   3. *Prosthetic Reconstructions*
      Clinical trials with implant systems utilizing new technologies to achieve effective host soft-tissue attachment to metal implants and promote extra-cortical bone bridging are ongoing. Advances and further research in bioengineering and biomaterials also relate to future directions for oncologic prosthetic reconstructions.

C. *Multimodality Management of Soft Tissue Sarcomas*: *Systemic Therapies for Metastases*
   The problem of metastases in patients with high-grade soft tissue sarcomas has not been eliminated and more effective cytotoxic drug regimens need development. With advances in understanding the molecular basis of soft-tissue sarcomas, genetically specific molecular therapy will, most likely, be the direction of the future.

D. *Metastatic Bone Disease*
   1. *Prevention of Skeletal Metastases*
      Future direction in clinical and laboratory research will focus on the prevention of skeletal metastases. In this context, prevention actually means prevention of the progression of microscopic disease or elimination of microscopic disease. Efforts will most likely focus on eliminating cancer-induced bone resorption and inhibiting cancer-induced angiogenesis. An alternative and perhaps equally valuable approach will be to develop novel therapies for eliminating areas of skeleton-residing microscopic cancer

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

2. *Assessment of pathologic fracture risk*
   Further study into the efficacy of whole body MRI and PET imaging for the detection of osseous metastases and response to treatment is needed.

IV. REFERENCES

American Association of Tissue Banking, Standards for Tissue Banking, 2002

Andela VB, Schwarz EM, Puzas JE, O'Keefe RJ, Rosier RN: Tumor metastasis and the reciprocal regulation of prometastatic and antimetastatic factors by nuclear factor kappaB. *Cancer Res* 2000;60:6557-6562.

Arvand A, Denny CT: Biology of EWS/ETS fusions in Ewing's family tumors. *Oncogene* 2001;20:5747-5754.

Baldini N, Scotlandi K, Serra M, et al: P-glycoprotein expression in osteosarcoma: a basis for risk-adapted adjuvant chemotherapy. *J Orthop Res* 1999;17:629-32.

Benassi MS, Molendini L, Gamberi G, et al: Involvement of INK4A gene products in the pathogenesis and development of human osteosarcoma. *Cancer* 2001;92:3062-3067.

Busch MP and Kleinman SH: Transfusion 40:140-149, 2000.

Chan HS, Grogan TM, Haddad G, DeBoer G, Ling V: P-glycoprotein expression: critical determinant in the response to osteosarcoma chemotherapy. *J Natl Cancer Inst* 1997;89:1706-1715.

Clohisy DR, Ly TV, Thompson RC, Jr: Fixation of large segment femoral allografts using plates augmented with cerclage wires. *Clin Orthop* 2000;198-205.

Cook GJ, Houston S, Rubens R, Maisey MN, Fogelman I: Detection of bone metastases in breast cancer by 18FDG PET: Differing metabolic activity in osteoblastic and osteolytic lesions. *J Clin Oncol* 1998;16:3375-3379.

Dion N, Sim FH: The use of allografts in orthopaedic surgery - part I: the use of allografts in musculoskeletal oncology. *J Bone Joint Surg Am* 2002;84-A:644-654.

Edmonson JH, Petersen IA, Shives TC, et al: Chemotherapy, irradiation, and surgery for function-preserving therapy of primary extremity soft tissue sarcomas: Initial treatment with ifosfamide, mitomycin, doxorubicin, and cisplatin plus granulocyte macrophage-colony-stimulating factor. *Cancer* 2002;94:786-792.

Friedlaender GE, Goldberg VM: *Approaches to the Retrieval and Banking of Osteochondral Allografts.* In Friedlaender GE, Tomford WW (eds): Bone and Cartilage Allografts: Biology and Clinical Applications. Park Ridge, IL, American Academy of Orthopaedic Surgeons, 1989, pp 185-192.

Gebhardt MC: What's new in musculoskeletal oncology? *J Bone Joint Surg Am* 2002;84-A:694-701.

Hazan EJ, Hornicek FJ, Tomford W, Gebhardt MC, Mankin HJ: The effect of adjuvant chemotherapy on osteoarticular allografts. *Clin Orthop* 2001;176-81.

Hornicek FJ, Gebhardt MC, Tomford WW, et al: Factors affecting nonunion of the allograft-host junction. *Clin Orthop* 2001;87-98.

Hornicek FJ, Gebhardt MC, Wolfe MW, et al: P-glycoprotein levels predict poor outcome in patients with osteosarcoma. *Clin Orthop* 2000;11-17.

Hortobagyi GN, Theriault RL, Porter L, et al: Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* 1996;335:1785-1791.

Jemal A, Thomas A, Murray T, Thun M: Cancer statistics, 2002. *CA Cancer J Clin* 2002;52:23-47.

Lewandrowski KU, Schollmeier G, Ekkemkamp A, Uhthoff HK, Tomford WW: Incorporation of perforated and demineralized cortical bone allografts. Part I: radiographic and histologic evaluation. *Biomed Mater Eng* 2001;11:197-207.

Lewandrowski KU, Schollmeier G, Ekkemkamp A, Uhthoff HK, Tomford WW: Incorporation of perforated and demineralized cortical bone allografts. Part II: A mechanical and histologic evaluation. *Biomed Mater Eng* 2001;11:209-219.

Mankin HJ, Gebhardt MC, Jennings LC, Springfield DS, Tomford WW: Long-term results of allograft replacement in the management of bone tumors. *Clin Orthop* 1996;86-97.

Ohlendorf C, Tomford WW, Mankin HJ: Chondrocyte survival in cryopreserved osteochondral articular cartilage. *J Orthop Res* 1996;14:413-416.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Park YB, Kim HS, Oh JH, Lee SH: The co-expression of p53 protein and P-glycoprotein is correlated to a poor prognosis in osteosarcoma. *Int Orthop* 2001;24:307-310.

Radig K, Hackel C, Herting J, et al.: Expression of P-glycoprotein in high grade osteosarcomas with special emphasis on chondroblastic subtype. *Gen Diagn Pathol* 1997;142:139-45.

Rosier RN, O'Keefe RJ, Teot LA, et al: P-glycoprotein expression in cartilaginous tumors. *J Surg Oncol* 1997;65:95-105.
Serra M, Maurici D, Scotlandi K, et al: Relationship between P-glycoprotein expression and p53 status in high-grade osteosarcoma. *Int J Oncol* 1999;14:301-307.

Strong DM, Friedlaender GE, Tomford WW, et al: Immunologic responses in human recipients of osseous and osteochondral allografts. *Clin Orthop* 1996;107-114.

Takeshita H, Kusuzaki K, Murata H, et al: Osteoblastic differentiation and P-glycoprotein multidrug resistance in a murine osteosarcoma model. *Br J Cancer* 2000;82:1327-1331.

Thompson RC, Jr., Garg A, Clohisy DR, Cheng EY: Fractures in large-segment allografts. *Clin Orthop* 2000;227-235.

Tomford WW, Mankin HJ: Bone banking. Update on methods and materials. *Orthop Clin North Am* 1999;30:565-570.

Traill Z, Richards MA, Moore NR: Magnetic resonance imaging of metastatic bone disease. *Clin Orthop* 1995;16:76-88.

U.S. Census Bureau, Statistical Abstracts of US 2001. Musculoskeletal allograft usage.

Wunder JS, Bull SB, Aneliunas V, et al: MDR1 gene expression and outcome in osteosarcoma: a prospective, multicenter study. *J Clin Oncol* 2000;18:2685-2694.

V. PANEL MEMBERS

Chair:	Mary O'Connor, MD	Mayo Clinic	Jacksonville, FL
Co-chair:	Mark Gebhardt, MD	Children's Hospital	Boston, MA
	Denis Clohisy, MD	Univ of Minnesota	Minneapolis, MN
	C. Parker Gibbs, MD	Univ of Florida	Gainesville, FL
	Randy Rosier, MD	University of Rochester	Rochester, NY
	Sean Scully, MD	Mayo Clinic	Rochester, MN

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel XIII: Infections

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Musculoskeletal orthopaedic infections can be both limb- and life-threatening. Postoperative wound infections occur in up to 1% of all clean orthopaedic surgical procedures. One percent of total joint replacements become infected and 2% to 3% of the total joint revisions become infected. Many of the orthopaedic joint infections require a two-stage procedure and the cost of these infections from a monetary and resource expenditure is very significant. In open fractures, the infection rate for Gustillo type I and II is reported as approximately 2% and for type III, the infection rate is generally reported from 10% to 30%.

B. *Importance to Public Health*
Because of the frequency of joint replacements, internal fixation of the spine and limb injuries, the economic burden imposed by infection as a complication, is significant.

II. RECENT ADVANCES

A. *Microvascular Muscle Transfers*
Use and refinement of soft tissue local and microvascular muscle transfers for coverage of bone and filling of dead space in open fractures, limb salvage in osteomyelitis, and for orthopaedic infections requiring muscle coverage.

B. *Antibiotic Bead Pouch*
The PMMA antibiotic bead pouch in the treatment of open fractures and antibiotic beads for orthopaedic infections and antibiotic spacers for infected total joints has been introduced.

The impact of these treatments in the management of open fractures, through the reduction of secondary contamination has been proposed.. In addition, antibiotic spacers or antibiotic articulating spacers have been used for the treatment of patients with an infected total joint arthroplasty. These approaches can provide an increased local antibiotic concentration in comparison to that achieved by the intravenous (IV) route. This may lead to a lower incidence of systemic side-effects, and may provides the potential for easier subsequent reconstructive procedures.

C. *Investigative Work on Biodegradable Antibiotic Beads*
Work on the elution properties of antibiotic beads, antibiotic spacers, and antibiotic transmission vehicles

D. *Elution Properties of Antibiotic Beads*
There has been significant work in the past decade in the elution properties of antibiotic beads, antibiotic spacers, and antibiotic transmission vehicles. Data has shown that elution levels are proportional to the following:

- antibiotic dosage
- antibiotic properties
- surface area
- fluid media
- rate of fluid turnover
- porosity of the transmission vehicle

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

E. *Use of Bone Transport Techniques to Treat Large Bone Defects*
Use of microvascular bone transfer (free fibular graft) to treat large bone defects has been developed.

F. *Glycocalyx (Biofilm)*
Identification and better understanding of glycocalyx (biofilm) and prevention of its formation is needed.

G. *Development of Vaccine for Hepatitis B*
This has had a significant impact in preventing hepatitis and is recommended for surgeons. Hepatitis B vaccine is also available for the general public.

H. *Antibiotics*
Newer antibiotic therapies have improved the treatment of patients with musculoskeletal infections. In particular, the quinolone family of antibiotics have been developed. This class of agents has enhanced the effectiveness of the oral administration option in patients with sensitive organisms.

Prior to the introduction of the quinolones, gram negative organisms usually required the use of intravenously administered antibiotics.

The new antibiotics Linezolid and Synercid have been found to be effective in the treatment of vancomycin-resistant enterococcus infections.

New oral anti-fungal agents have been developed. These are particularly important in the treatment of immuno-compromised patients. In the past, these infections were treated with amphotericin. Amphotericin has the potential for significant renal complications.

I. *Polymerase Chain Reaction (PCR)*
Investigative work with polymerase chain reaction (PCR) for early detection and identification of musculoskeletal infections.

III. FUTURE DIRECTION OF RESEARCH

A. Continued work on biodegradable materials for antibiotic delivery.

B. Work on immunizations, including passive antibacterial vaccines (for Staphylococcal, Anthrax, etc).

C. Continued study of glycocalyx biofilm.

D. Investigate the impact of granulocyte stimulating hormone on clinical infection.

E. New strategies for eradication of bacteria without antibiotics.

F. Gene therapy to alter bacterial resistant organisms, to treat infections and to stimulate fracture healing and filling for bone defects.

G. Develop implant materials that will inhibit infection and reduce the chance of infection about implanted devices.

H. Determine methods that will lead to early and accurate detection of infection.

I. Investigate the cause(s) of and develop preventative strategies to reduce the potential for implant infection

J. Develop and explore the use of biodegradable antibiotic delivery systems.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

K. Study of bacterial mechanisms of producing disease to determine new ways to attack or eliminate bacterial infections.

L. Evaluate the preliminary finding that some organisms have the ability to enter cells and gain protection from certain antibiotics.

IV. REFERENCES

Costerton JW, Stewart PS: Battling biofilms. *Scientific American* 2001;285(1), 74-81.

Einhorn TA, Lee CA: Bone regeneration: New findings and potential clinical applications. *J Am Acad Orthopaedic Surgeons* May/June 2001;9(3):157-164.

Evans RP, Nelson CL, Bowen WR, Kleve MG, Hickmon SG: Visualization of bacterial glycocalyx with a scanning electron microscopy. *Clin Orthop* February 1998;347:243-249.

Fitzgerald RH Jr., Ruttle PE, Arnold PG, et al: Local muscle flaps in the treatment of chronic osteomyelitis. *JBJS* 1985;67:175.

Garvin KL, Miyano JA, Robinson D, et. al.: Polylactide/polyglycolide antibiotic implants in the treatment of osteomyelitis: A canine model. *J Bone Joint Surg* (Am) 1994;76:1500-1506.

Greene N, Holtom PD, Warren CA, et. al.J: In vitro elution of tobramycin and vancomycin polymethylmethacrylate beads and spacers from simplex and palacos. *Amer J of Orthopaedics*, March 1998;XXVII (3):201-205.

Han C-S, Wood MB, Bishop AT, Cooney III WP: Vascularized bone transfer. *J of Bone and Joint Surgery*, 1992;74-A(10):1441-1449.

Lee WM: Hepatitis B virus infection. *New England Journal of Medicine* Dec11;1997;337(24):1733-1745.

McNeil SA, Clark NM, Chandrasekar PH, Kauffman CA: Successful treatment of vancomycin-resistant enterococcus faecium bacteremia with linezolid after failure of treatment with synercid (Quinupristin/Dalfopristin). *Clinical Infectious Diseases* February 2000;30(2):403-404.

Nelson CL, Evans RP, Blaha JD, et. al.: A comparison of gentamicin-impregnated polymethylacrylate bead implantation to conventional parenteral antibiotic therapy in infected total hip and knee arthroplasty. *Clin Orthop* 1993;295:96-101.

Nelson CL, Hickmon SG, Skinner RA: Treatment of experimental osteomyelitis by surgical debridement and the implantation of bioerodable, Polyanhydride-Gentamicin beads. *J Orthopaedic Research* 1997;15(2):249-255.

Sowa DT, Weiland AJ: Clinical Applications of Vascularized Bone Autografts, Orthopedic Clinics of North America, April 1987;18(2):257-273.

V. PANEL MEMBERS

Chair:	Michael J. Patzakis, MD	University of Southern California	Los Angeles, CA
Co-Chairman:	Carl Nelson, MD	University of Arkansas for Medical Sciences	Little Rock, AR
	Michael Busch, MD	Children's Orthopaedics of Atlanta	Atlanta, GA
	Jason Calhoun, MD	Univ. of Texas Medical Branch	Galveston, TX
	Arlen Hanssen, MD	Mayo Clinic	Rochester, MN
	Paul Holtom, MD	University of Southern California	Los Angeles, CA
	L. Scott Levin, MD	Duke University Medical Center	Durham, NC
	Adelisa Panlilio, MD	Centers for Disease Control	Atlanta, GA
	Mark Triffon, MD	Ohio State University	Columbus, OH
	Jerome Wiedel, MD	Univ of Colorado Health Sciences Ctr	Aurora, CO

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel XIV: Sports, Fitness and Ligaments

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*

Fitness, as generally understood, is a term encompassing an array of health-related activities leading to optimal body size and shape, sensory acuity, resistance to disease and disorders, optimal body functioning, optimal recuperative ability, and the ability to perform physical and mental tasks efficiently. These goals are achieved through optimum cardio-respiratory function, including optimal aerobic capacity with efficient oxygen transport and delivery. Achievement of fitness, as described, requires daily exercise. The exercise requirements vary necessarily with age and individual comorbidities, but require both aerobic and resistance exercises. Fitness is associated with good health and a sense of well being, but accumulated evidence has demonstrated convincingly that low levels of physical activity are associated with high cardiovascular mortality, high total mortality, as well as increased incidence of type ii diabetes mellitus, hyperlipidemia, hypertension, obesity, and mental depression—to offer just a short list of inactivity-related comorbidities.

The heart is a muscle that must be exercised to be strengthened. The World Health Organization has declared physical inactivity to be among the most important risk factors threatening global health, possibly as detrimental to health as smoking. In addition to the prevention of adverse physiological effects, exercise is an effective antidepressant, and probably minimizes cognitive decline associated with aging by improving cerebral circulation.

In a study of 85,000 nurses, weight control stood out as perhaps the most important life style factor in preventing type II diabetes. Sixty percent of the cases of diabetes in this group could be traced to excess weight as defined by BMI (Body Mass Index) > 25. Regular exercise as well as a good diet are essential requirements to control BMI. Even in the absence of weight loss, however, exercise cut the diabetes risk 24%. Further evidence was adduced from the NIH Diabetes Prevention Study showing that even in the absence of weight loss, 30 minutes of physical activity per day (walking or biking) reduced the diabetes risk 58%.

Physical activity required to achieve fitness need not be of the gym type with exercise equipment, but includes activities performed with vigor - such as housework, gardening, or brisk walking (3.5-4 mph). The 1996 Surgeon General's report disclosed that significant health benefits could be obtained with 30 minutes of such exercise per day. These exercise periods need not be consecutive, that is, 10 minutes three times per day should be sufficient.

B *Importance to Public Health*

The scope of the research in this area is to better define the activity levels needed to:

1) maintain fitness in the various age groups, and in men and women,
2) maintain the highest level of fitness possible in the wide range of individuals compromised from typical exercise schedules through matters of illness, or physical disability,
3) maintain fitness and safely achieve peak performance of individual athletes in the wide variety of sport activities.

The research also needs to focus on tools, techniques, and products to prevent injuries and to facilitate recovery from injuries to the neuro-musculoskeletal system.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

II. RECENT ADVANCES

A. *Adaptive Responses to Physical Training*
Numerous adaptive responses take place with physical training. These adaptations have been shown to result in a more efficient system for oxygen transfer to muscle, resulting in muscles that are then able to better utilize unlimited lipid stores available in the system to them, rather than the limited carbohydrate reserves available. This response contributes to higher levels of fitness and well being in both genders and in all age groups.

B. *Gender Differences in Endurance Training*
Gender differences in the physiology of endurance training have focused on fluid and electrolyte balance, especially with respect to replacement during and after exercise. Certain dietary considerations have also been shown to be gender specific, such studies finding the thin dieting female especially at risk for the "female athlete triad" of disordered eating, amenorrhea and osteoporosis. Specific recommendations have been made with respect to trace elements, protein, fat and caloric needs of ultra-endurance athletes as well as the particular needs of elderly exercising individuals.

C. *"Blood Doping" Research*
The anemia of athletes has been shown to result from a variety of causes including hemodilution, haemolysis (heel strike anemia), hematuria, and intestinal bleeding. Iron stores have been shown to be depleted in some cases, resulting in the need for dietary consultation and possible supplementation with iron. Alleged improvements in athletic performance following "blood doping" with exogenous erythropoietin has the potential for increased viscosity of the blood and subsequent thrombosis with potentially fatal results.

D. *Research into Factors Impacting Health Risks from Obesity*
Obesity has been shown historically to be a risk factor for type II diabetes, hypertension, hyperlipidemia, atherosclerosis, osteoarthritis and acute cardiovascular events such as myocardial infarction, and stroke. In recent years regular exercise has been shown to be important in the management of obesity. New evidence suggests that management of diet and exercise should focus on metabolic profiles such as triglyceride levels and HDL/LDL levels rather than weight loss alone to control risk factors enumerated above. Racial differences in prevalence of obesity have been noted among African-American women. This makes it likely that they bear a disproportionate burden of the comorbidities attributable to obesity. The US Centers of Disease Control and Prevention (CDC) have worked with regional racially focused groups to provide information about the elements of diet and physical activity required for preventing obesity.

E. *Aging and Resistance Training*
The concomitant losses of skeletal muscle and bone mass along with gradual accretion of adipose tissue have been noted to typify usual human aging. Resistance training in the elderly during hypocaloric dieting has been noted to augment lean mass while further reducing fat mass.

F. *Connective Tissue Research:*
As with general physical fitness, connective tissue cells rely heavily upon mechanical input to maintain homeostasis. Early studies documented the serious effects of stress deprivation on connective tissue. Recent studies have focused on the mechanisms involved in mechanical transduction of cellular signaling leading to ultimate connective tissue health. Examples are listed below:

1. Even short periods of immobilization (inactivity) result in an up regulation of collagenase expression in ligament and tendons. This is inhibited by tensile loading in a dose-dependent manner. This information stresses the importance of early active tensile loading of reconstructive ligaments and tendons.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

2. Tensile loading of tendons produces nuclear deformation and calcium signaling in tendon cells in situ. This observation provides a mechanism for a mechanotransduction pathway for stress-induced cell signaling.

3. Cyclic tensile loading produces an up regulation of stress-activated protein kinases in tendon cells. The stress response is amplitude dependent but not frequency dependent. This mechano-transduction pathway may play a role in the etiology of overuse injuries in tendons.

4. Cell stretching activates a wide variety of gene expression in tendon cells.

G. *Ligament Function and Healing*

Advances in understanding of ligament function and healing have continued at both clinical and basic research levels:

1. The ACL (anterior cruciate ligament) injury continues to receive vigorous basic and clinical research emphasis because of the devastating nature of the injury to the sports enthusiasts at all levels as well as to individuals employed in occupations requiring moderate, but repetitious physical effort. Unlike many other ligaments, the ACL does not heal spontaneously, even if primarily repaired and protected post operatively. Furthermore, bracing offers only partial restoration of pre-injury function, hence surgical correction is usually required for the individual with disabling instability. Major advances in diagnosis of knee injuries have evolved over the past decade with better understanding of the mechanisms of injury, better understanding of the biomechanical basis of the resultant instability, and through application of objective tools of assessment. In particular, the ready availability of magnetic resonance imaging has added measurably to the objective global assessment of the constellation of injuries associated with ACL tears. Surgical management has made similar dramatic strides, aided by endoscopic technology, permitting a “virtual surgery” methodology to help guide the surgeon. Outcome assessments after ACL reconstruction are generally positive, with typical outcomes from major centers reporting 90% good and excellent results.

2. A perplexing observation concerns the high rate of ACL tears in women participating in similar sports activities to men. The reported rate of injuries to the ACL in women is between two and eight times that in men. No contact mechanisms appear to predominate in the ACL tears in the female athletes. There is lack of agreement about the factors responsible for the higher incidence of these injuries. There are probably multiple causative factors. Possible contributing factors include the higher quadriceps angle in women, a narrower intercondylar notch, greater joint laxity, hormonal influences and differences in muscle strength and coordination between the sexes. While evidence is not yet conclusive, reports of increased ACL tears during days 10-14 of the menstrual cycle when estrogen levels peak have focused attention on this element of the puzzle. It is speculated that fibroblast cell surface receptors for estrogen may play a role in the increased incidence of ACL injuries in females.

H. *Lower Body Positive Pressure (LBPP) and Healing*

Studies have documented the comfortable and safe musculoskeletal unloading effect of lower body positive pressure (LBPP), which may be useful in rehabilitation programs. This new concept of rehabilitation should facilitate earlier return to normal daily activities in a wide spectrum of patients who require decreased lower extremity weight-bearing following surgery.

I. *Muscle Physiology*

Advances in research on muscle physiology with important clinical implications include:

1. It has now been convincingly demonstrated that muscle sarcomere number adjustment after chronic immobilization or surgical tendon transfer is much more complicated than previously believed. Whereas it had been thought that sarcomere number always optimized to the new position, this has clearly been shown not to be true in two animal

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

models that mimic the clinical situation closely. Based on the wide range of sarcomere length operating ranges that have been recently reported, it is clear that surgeons must take greater care in setting muscle length and, consequently, sarcomere length, during surgical tendon transfer procedures.

2. Recovery of function in spinal cord-injured patients has been demonstrated to occur even in the case of complete cord lesions. This has been convincingly demonstrated in human subjects who, by measuring both joint kinematics and muscular electrical activity, have shown that the spinal cord itself can "learn" movements and make significant adjustments to motor output patterns even in the absence of higher input from the motor cortex.

3. Muscle passive elasticity, once thought to be based on membrane mechanical properties, is now clearly shown to be due to the largest protein ever identified, aptly named "titin." This protein, originally suspected to exist based on mechanical and morphological measurements, has been partially cloned and sequenced and single molecule experiments have been performed using atomic force microscopy. Recent discoveries have implicated alterations in titin properties to the stiffness that occurs in "spastic" skeletal muscle secondary to cerebral palsy, stroke, and head injury.

4. The cellular signaling pathway that controls muscle hypertrophy has been shown to involve the calcium-activated protein, calcineurin. Based partially on these studies, a novel isoform of the Insulin-like growth factor (IGF) specific to muscle, named mechano-growth factor. These discoveries, while very basic, have tremendous potential in the field of rehabilitation and recovery from sarcopenia.

5. Noninvasive imaging of skeletal muscle during normal function has been accomplished using real-time ultrasound. These imaging methods have recently been used to study the normal and aged human Achilles tendon and promises to improve our understanding and treatment of human tendon pathophysiology.

III. FUTURE DIRECTION IN RESEARCH

A. *Fitness Requirements for Demographic Groups*
Development of better understanding of the particular fitness requirements for different genders, for different age groups, and for individuals with different physical impairments.

B. *Impact of Inactivity*
Development of better understanding of the impact of inactivity with respect to common pathologic mechanisms in cardiovascular, musculoskeletal, and neurologic diseases or disorders.

C. *Pathomechanics of Joint Injury*
1. Development of better understanding of the pathomechanics of joint injury
2. Development of more effective protective devices for particular sports where risks of physical impairment exist.

D. *Improved Training and Conditioning Programs*
Development of improved training and conditioning programs that can improve muscle reaction time, protective muscle stiffness, and performance.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

E. *Gender Differences in Ultra-Performance Sports*
Development of better understanding of gender differences in ultra-performance sports that can lead to focused programs of prevention of disorders associated with high-performance athletes.

F. *Exercise Impact on Osteoporosis*
Development of concepts leading to guidance to the general population in all age groups for reducing the risk of osteoporosis by optimizing weight-bearing exercise protocols and resistance-training protocols.

G. *In Vivo Forces on Soft Tissues*
Development of better understanding of the forces in the normal and healing soft tissues during in vivo activities. Development of new designs based on this understanding for improved repair and reconstruction procedures as well as for scientifically based rehabilitation protocols.

H. *Signaling Pathways*
Identification of the signaling pathways involved with muscle, tendon and ligament injury, repair, and hypertrophy.

I. *Study of Magnetic Resonance Imaging (MRI) Metabolic Signaling*
Determination of the metabolic events associated with the signals generated by magnetic resonance imaging (MRI) and determination of the structures responsible for the signal intensities observed with ultrasound imaging of muscle. Application of these methodologies to the study of muscle-tendon and ligament physiology and pathophysiology.

J. *Spastic Skeletal Muscle Research*
Determination of the mechanical and biological factors responsible for sarcomere number changes in normal, transferred and spastic muscle, and characterization of the structural basis for increased stiffness of spastic skeletal muscle.

K. *Fitness Training for the Disabled*
Special attention should be made concerning the needs for fitness training of the disabled. Particular disabilities need to be addressed independently because of the wide ranging nature of the underlying deficits. Each disability subset will require independent assessment and recommendation regarding fitness training goals.

L. *Fitness Training for the Elderly*
Similarly, special attention should be addressed to the needs for fitness training in the elderly. A decade by decade analysis of the recommendations for training for the average individual will be necessary.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

V. REFERENCES

Akeson WH, Amiel D, LaViolette D: The connective-tissue response to immobility: a study of the chondroitin-4 and 6-sulfate and dermatan sulfate changes in periarticular connective tissue of control and immobilized knees of dogs. *Clin Orthop* 1967;51:183.

Amiel D, Akeson WH, Harwood FL, Mechanic GL: The effect of immobilization on the types of collagen synthesized in periarticular connective tissue. *Connect Tissue Res* 1980;8(1):27.

Arnoczky S, Tian T, Lavagnino M: Tensile load modulates inhibition of MMP-1 expression in tendons. World Congress of Biomechanics, 2002.

Arnoczky SP, Lavagnino M, Whallon JH, Hoonjan A: In situ cell nucleus deformation in tendons under tensile load; a morphological analysis using confocal laser microscopy. *J Orthop Res* 2002;20(1):29.

Burkholder TJ, Lieber RL: Sarcomere length operating range of vertebrate muscles during movement. *J Exp Biol* 2001;204(Pt 9):1529.

Chatard JC, Mujika I, Guy C, Lacour JR: Anemia and iron deficiency in athletes. Practical recommendations for treatment. *Sports Med* 1999;27(4):229.

Dietz W: Focus group data pertinent to the prevention of obesity in African Americans. *Am J Med Sci* 2001;322(5):275.

Erikssen G: Physical fitness and changes in mortality: the survival of the fittest. Sports Med 31(8):571, 2001.

Fodor JG, Adamo KB: Prevention of type 2 diabetes mellitus by changes in lifestyle. N Engl J Med 345(9):696; discussion 696, 2001.

Frank CB, Jackson DW: The science of reconstruction of the anterior cruciate ligament. *J Bone Joint Surg Am* 1997;79(10):1556.

Friden J, Ponten E, Lieber RL: Effect of muscle tension during tendon transfer on sarcomerogenesis in a rabbit model. *J Hand Surg Am* 2000;25(1):138.

Griffin LY, Agel J, Albohm MJ, et. al.: Noncontact anterior cruciate ligament injuries: risk factors and prevention strategies. *J Am Acad Orthop Surg* 2000;8(3):141.

Harkema SJ, Hurley SL, Patel UK, et. al.: Human lumbosacral spinal cord interprets loading during stepping. *J Neurophysiol* 1997;77(2):797.

Harner CD, Fu FH, Irrgang JJ, Vogrin TM: Anterior and posterior cruciate ligament reconstruction in the new millennium: A global perspective. *Knee Surg Sports Traumatol Arthrosc* 2001;9(6):330.

Kell RT, Bell G, Quinney A: Musculoskeletal fitness, health outcomes and quality of life. Sports Med 31(12):863, 2001.

Majima T, Marchuk LL, Shrive NG, Frank CB, Hart DA: In-vitro cyclic tensile loading of an immobilized and obilized ligament autograft selectively inhibits mRNA levels for collagenase (MMP-1). *J Orthop Sci* 2000;5(5):503.

Manore MM: Nutritional needs of the female athlete. Clin Sports Med 18(3):549, 1999.

Murray CJ, Lopez AD, Jamison DT: The global burden of disease in 1990: summary results, sensitivity analysis and future directions. Bull World Health Organ 72(3):495, 1994.

Pendergast DR, Leddy JJ, Venkatraman JT: A perspective on fat intake in athletes. *J Am Coll Nutr* 2000;19(3):345.

Poirier P, Despres JP: Exercise in weight management of obesity. Cardiol Clin 19(3):459, 2001.

Rankin JW: Role of protein in exercise. *Clin Sports Med* 1999;18(3):499.

Singh MA: Combined exercise and dietary intervention to optimize body composition in aging. *Ann N Y Acad Sci* 1998;854:378.

Surgeon General's report on physical activity and health. From the Centers for Disease Control and Prevention. Jama 276(7):522., 1996.

Voss LA, Fadale PD, Hulstyn MJ: Exercise-induced loss of bone density in athletes. J Am Acad Orthop Surg 6(6):349, 1998.

Wojtys EM, Ashton-Miller JA, Huston LJ: A gender-related difference in the contribution of the knee musculature to sagittal-plane shear stiffness in subjects with similar knee laxity. *J Bone Joint Surg Am* 2002;84-A(1):10.

Wojtys E, Huston L, Lindenfeld T, al e: Association between the menstrual cycle and ACL injuries in female athletes. *AM J Sports MED* 1998;26:614.

Woo SL, Matthews JV, Akeson WH, Amiel D, Convery FR: Connective tissue response to immobility. Correlative study of biomechanical and biochemical measurements of normal and immobilized rabbit knees. *Arthritis Rheum* 18(3):257, 1975.

Zachwieja JJ, Yarasheski KE: Does growth hormone therapy in conjunction with resistance exercise increase muscle force production and muscle mass in men and women aged 60 years or older? *Phys Ther* 1999;79(1):76.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

V. PANEL MEMBERS

Chair:	Wayne Akeson, MD	Univ of California, San Diego	San Diego, CA
	Steve Arnoczky, DVM	Michigan State University	East Lansing, MI
	Cyril B. Frank, MD	Univ of Calgary	Calgary, Alberta, Canada
	Robert J. Johnson, MD	Univ of Vermont	Burlington, VT
	Richard Lieber, MD	Univ of California, San Diego	San Diego, CA
	John Richmond, MD	New England Medical Center	Boston, MA
	James Tibone, MD	Univ of Southern California	Los Angeles, CA
	Ed Wojtys, MD	Univ of Michigan	Ann Arbor, MI
	Savio Woo, MD	Univ of Pittsburgh Med Ctr	Pittsburgh, PA

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel XV: Bioengineering and Biomaterials

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Bioengineering's importance to orthopaedic surgery is the application of and results of collaboration to solve clinical problems and apply engineering advances to the musculoskeletal system. Over the past two decades there has been an explosion of activity that has enhanced our understanding of the behavior of the musculoskeletal tissues (bone, cartilage, ligament, muscle, and tendon) and their ability to provide long-term function for the human skeleton. Orthopaedic bioengineering and biomaterials research has continued to refine our understanding of how natural tissues function in normal activities of living, and how new structures and materials can be designed, manufactured, and implanted to replace those functions when disease, injury, or other forces lead to compromise in these functions. Thus the world of orthopaedic bioengineering and biomaterials encompasses a broad range of tissues and functions that the orthopaedic surgeons and their patients encounter.

B. *Importance to Public Health*
Recent advances in bioengineering and biomaterials have had substantial impact in multiple areas of musculoskeletal structure and function. These areas are the following: joint replacement; fracture fixation and management; spinal stabilization for arthritis and disc disorders; joint stabilization tissues and devices, both external and internally applied; new approaches to realignment and application of devices to musculoskeletal tissues using robotics and computer-controlled navigation systems.

II. RECENT ADVANCES

A. *Fixation*
New fixation approaches to devices (uncemented fixation): Porous metal technology and its application to hip and knee reconstructive surgery widely expanded the uses and longevity of implants. Its maturation has resulted in predictable implant technologies and has led to advances in hydroxyapatite technology and usage and more recently development of porous tantalum technology.

B. *Bearing Materials*
1. New bearing materials /improved bearing materials: As fixation technology and techniques improved, wear of bearing surfaces emerged as a central problem area in the long term performance of implants and surrounding tissue. New lower wear couples, such as the new highly cross-linked polyethylenes for total hip arthroplasty, metal-metal, and ceramic-ceramic couples have been recently introduced for clinical usage. Preventing bone loss from the osteolytic process, and addressing it surgically with appropriate biological and biomechanical solutions continue to be areas of strong product and technique development.

2. Joint simulation and wear testing of new materials: Clinical safety of new materials and focused and accelerated market introduction have required substantive improvements in pre-clinical testing approaches. Simulations to predict wear behavior of materials and component parts have accelerated our understanding of failure modes of acetabular components, focusing efforts to provide alternatives.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

C. *Joint Replacement*

1. Three-dimensional imaging for implant design and demographic mapping: The need for more precise implants and devices to address complex or unique diseases spawned a custom approach that demanded and led to the development of new and improved imaging capabilities.

2. Kinematic analysis of normal, diseased and replaced joints: Substantial growth in the ability to measure clinically important kinematic information from normal, diseased, and repaired joints has advanced our understanding of mechanical patterns of failure and success. This has allowed surgeons and the orthopaedic industry to identify technologies and techniques to more accurately repair damaged joints.

3. Three-dimensional imaging and application of robotics to implantation, surgical navigation and implant manufacturing: The initial application of 3-dimensional technologies to the development of implants had identified multiple additional applications of technologies where precision of implantation may improve long-term performance of devices and other reconstructions.

4. Application of joint replacement concepts to multiple sites, including the shoulder, elbow, wrist, finger, hip, knee, and ankle: As the joint replacement market of the lower extremities has matured, the large volume of information and improvements in technology associated with these joints has found ready application in most other joints.

5. Development of bioresorbable implants: By applying advances in polymer chemistry and polymer materials science, a new generation of orthopaedic implants are currently in use or are under development. These implants have the ability to be degraded by the host after they have served their temporary function(s) as a scaffold or internal fixation device.

D. *Patient Quality of Experience*

Improved interactions of scientific, clinical, and industrial communities to improve the quality of patient experience and results of interventions: The strong interconnections of scientific and clinical communities with the industry that derives new technologies in musculoskeletal care has put additional responsibility on all parties to develop mechanisms of interaction that focus on improving the quality of the patient experience and results of intervention, and provided timely and appropriate introduction to the market. The AAOS established the Orthopaedic Device Forum, which has led the way among medical specialties in identifying mechanisms to achieve rapid and effective product introduction while ensuring the safety of the population it serves.

E. *DEXA Imaging*

Dual-Energy X-Ray Absorptiometry (DEXA) imaging of bone quality and bone remodeling in diseased and replaced joints: As DEXA imaging technologies to study the quality of bone, particularly important to the prevention and treatment of osteoporosis and its consequences, these technologies have found application in enhancing our understanding of bone behavior in diseased and replaced joints.

F. *Research on Thermal Energy in Soft-Tissue Disorders*

Application of thermal energy to treat soft-tissue disorders: Thermal energy delivered by either radio frequency or laser modalities has been used to treat shoulder instability, disc degeneration, and other disorders which afflict musculoskeletal soft tissues.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

G. *Advances in Prosthetics*
The performance of upper and lower extremity prosthetic devices continues to improve with the use of lighter-weight composite materials and by virtue of advances in microchip technology. Current devices are now able to perform more complex functions and have the capability for sensory and tactile feedback.

III. FUTURE DIRECTION OF RESEARCH

A. *Materials*
1. Wear
   a. Understand and reduce interaction of prosthetic material with host
   b. Develop and refine early detection methodologies
   c. Develop models of early intervention to minimize sequella of wear
2. Prevention of Implant Failure
   a. Prosthetic design improvements
   b. Medical therapies to reduce failures
   c. Laboratory assessments of by-products
   d. Metallic ion effect on tissues and patients
   e. Approaches to minimize the production of debris particles
   f. Identify molecular markers of loosening/osteolysis

B. *Fixation*
New coatings to improve implant fixation.

C. *Kinematics*
1. Hip joints/ Knee/ Spine
2. Normal
3. Diseases
4. Repaired

D. *Imaging Technologies*
1. Radiographic evaluation of fixation- (Roentgen Stereophotogrammetric Analysis) RSA
2. Radiographic evaluation of remodeling- DEXA
3. Radiographic evaluation of wear
4. Improved implantation technologies- Image Guided Surgery (Surgical Navigation)
5. Robotic surgical techniques
6. Tele-surgery
7. Instrumentation for minimally invasive surgery

E. *Modeling*
1. Requirement of Finite Element Analysis (FEA) to predict implant performance
2. Modeling to identify fundamental mechanisms of failure and to predict performance failure of mechanical devices

F. *Performance Measurement*
1. Match clinical requirements with device performance
2. Factors influencing rate of recovery of joint, bone, tendon and/or muscle injury
3. The role of devices, implants, or biologically active materials and improved understanding of kinematics in expediting recovery
4. Measuring biological and biomechanical device performance
5. Development of high-speed computational methodologies to simulate natural and artificial joint performance

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

G. *Cellular Mechanics*
Apply basic principles of the mechanics of materials to individual connective tissue cells to define the cell response to mechanical stimuli and the cellular pathways involved in the transduction of mechanical inputs.

IV. REFERENCES

Fixation

Archibeck MJ, Berger RA, Jacobs JJ, et. al.: Second-generation cementless total hip arthroplasty: eight to eleven year results. *J Bone Joint Surg Am* 83-A(11):1666-1673, 2001.

Christie MJ, DeBoer DK, Tingstad EM, et. al.: Clinical experience with a modular noncemented femoral component in revision total hip arthroplasty: 4- to 7-year results. *J Arthroplasty* 15(7):840-848, 2000.

Cruz-Pardos A, Garcia-Cimbrelo E: The Harris-Galante total hip arthroplasty: A minimum 8-year follow-up study. *J Arthroplasty* 16(5):586-597, 2001.

D'Lima DD, Yashar AA, Venn-Watson EJ, Colwell CW Jr, Walker RH: The Harris-Galante Porous acetabular component at intermediate follow-up. *Orthopedics* 24(8):747-751, 2001.

Dunkley AB, Eldridge JD, Lee MB, Smith EJ, Learmonth ID: Cementless acetabular replacement in the young. A 5- to 10-year prospective study. *Clin Orthop* Jul(376):149-155, 2000.

Hofmann AA, Feign ME, Klauser W, VanGorp CC, Camargo MP: Cementless primary total hip arthroplasty with a tapered, proximally porous-coated titanium prosthesis: a 4- to 8-year retrospective review. *J Arthroplasty* 15(7):833-839, 2000.

Jana AK, Engh CA Jr, Lewandowski PJ, Hopper RH Jr, Engh CA: Total hip arthroplasty using porous-coated femoral components in patients with rheumatoid arthritis. *J Bone Joint Surg Br*83(5):686-690, 2001.

Kawamura H, Dunbar MJ, Murray P, Bourne RB, Rorabeck CH: The porous coated anatomic total hip replacement. A ten to fourteen-year follow-up study of a cementless total hip arthroplasty. *J Bone Joint Surg Am* 83-A(9):1333-1338, 2001.

Keisu KS, Orozco F, McCallum JD 3rd, et. al.: Cementless femoral fixation in the rheumatoid patient undergoing total hip arthroplasty: minimum 5-year results. *J Arthroplasty* 16(4):415-421, 2001.

Kligman M, Kirsh G: Hydroxyapatite-coated total hip arthroplasty in osteoporotic patients. *Bull Hosp Jt Dis* 59(3):136-139, 2000.

McNally SA, Shepperd JA, Mann CV, Walczak JP: The results at nine to twelve years of the use of a hydroxyapatite-coated femoral stem. *J Bone Joint Surg Br* 83(3):461, 2001.

Suh KT, Lee CB, Kim IJ: Natural progress of a bone scan after cementless hydroxyapatite-coated total hip arthroplasty. *Clin Orthop* Aug(389):134-142, 2001.

Tanzer M, Kantor S, Rosenthall L, Bobyn JD: Femoral remodeling after porous-coated hip arthroplasty with and without hydroxyapatite-tricalcium phosphate coating: A prospective randomized trial. *J Arthroplasty* 16(5):552-558, 2001.

Tonino A, Oosterbos C, Rahmy A, Therin M, Doyle C: Hydroxyapatite-coated acetabular components. Histological and histomorphometric analysis of six cups retrieved at autopsy between three and seven years after successful implantation. *J Bone Joint Surg Am* 83-A(6):817-825, 2001.

Yamaguchi K, Masuhara K, Ohzono K, et. al.: Evaluation of periprosthetic bone-remodeling after cementless total hip arthroplasty. The influence of the extent of porous coating. *J Bone Joint Surg Am* 82-A(10):1426-1431, 2000.

Bearing Materials

Baker DA, Hastings RS, Pruitt L: Study of fatigue resistance of chemical and radiation crosslinked medical grade ultrahigh molecular weight polyethylene. *J Biomed Mater Res* 46(4):573-581, 1999.

Beaule PE, Campbell P, Mirra J, Hooper JC, Schmalzried TP: Osteolysis in a cementless, second generation metal-on-metal hip replacement. *Clin Orthop* May(386):159-165, 2001.

Bizot P, Nizard R, Lerouge S, Prudhommeaux F, Sedel L: Ceramic/ceramic total hip arthroplasty. *J Orthop Sci* 5(6):622-627, 2000.

Boehler M, Plenk H Jr, Salzer M: Alumina ceramic bearings for hip endoprostheses: the Austrian experiences. *Clin Orthop* Oct(379):85-93, 2000.

Chiesa R, Tanzi MC, Alfonsi S, et. al.: Enhanced wear performance of highly crosslinked UHMWPE for artificial joints. *J Biomed Mater Res* 50(3):381-387, 2000.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Edidin AA, Pruitt L, Jewett CW, et. al.: Plasticity-induced damage layer is a precursor to wear in radiation-cross-linked UHMWPE acetabular components for total hip replacement. Ultra-high-molecular-weight polyethylene. *J Arthroplasty* 14(5):616-627, 1999.

Garino JP: Modern ceramic-on-ceramic total hip systems in the United States: early results. *Clin Orthop* Oct(379):41-47, 2000.

Grobbelaar CJ, du Plessis TA, Marais F: The radiation improvement of polyethylene prostheses. A preliminary study. *J Bone Joint Surg Br* 60-B(3):370-374, 1978.

Haraguchi K, Sugano N, Nishii T, et. al.: Analysis of survivorship after total hip arthroplasty using a ceramic head. *Clin Orthop* Oct(391):198-209, 2001.

Jazrawi Lm, Adler EM, Jazrawi AJ, Jaffe WL: Radiographic comparison of grit-blasted hydroxyapatite and acr-deposited hydroxyapatite acetabular components. A four-year follow-up study. *Bull Hosp Jt Dis* 59(3):144-148, 2000.

Kim, YH, Kim JS, Cho SH: A comparison of polyethylene wear in hips with cobalt-chrome or zirconia heads. A prospective, randomized study. *J Bone Joint Surg Br* 83(5):742-750, 2001.

Kurtz SM, Pruitt LA, Jewett CW, Foulds JR, Edidin AA: Radiation and chemical crosslinking promote strain hardening behavior and molecular alignment in ultra high molecular weight polyethylene during multi-axial loading conditions. *Biomaterials* 20(16):1449-1462, 1999.

McKellop HA: Bearing surfaces in total hip replacements: state of the art and future developments. *Instr Course Lecture* 50:165-179, 2001.

McKellop H, Shen FW, Di Maio W, Lancaster JG: Wear of gamma-crosslinked polytethylene acetabular cups against roughened femoral balls. *Clin Orthop* Dec(369):73-82, 1999.

Oonishi H, Wakitani S, Murata N, et. al.: Clinical experience with ceramics in total hip replacement. *Clin Orthop* Oct(379):77-84, 2000.

Rieker C, Konrad R, Schon R: In vitro comparison of the two hard-hard articulations for total hip replacements. *Proc Inst Mech Eng*: 215, 2001.

Urban JA, Garvin KL, Boese Ck, et. al.: Ceramic-on-polyethylene bearing surfaces in total hip arthroplasty: Seventeen to twenty-one-year results. *J Bone Joint Surg Am* 83-A(11):1688-1694, 2001.

Wagner M, Wagner H: Medium-term results of a modern metal-on-metal system in total hip replacement. *Clin Orthop* Oct(379):123-133, 2000.

Joint Simulation

Clarke IC, Good V, Williams P, et. al.: Ultra-low wear rates for rigid-on-rigid bearings in total hip replacements. *Proc Inst Mech Eng* 214(4):331-347, 2000.

DesJardins JD, Walker PS, Haider H, Perry J: The use of force-controlled dynamic knee simulator to quantify the mechanical performance of total knee replacement designs during functional activity. *J Biomech* 33(10):1231-1242, 2000.

Firkins PJ, Tipper JL, Ingham E, et. al.: A novel low wearing differential hardness, ceramic-on-metal hip joint prosthesis. *J Biomech* 34(10):1291-1298, 2001.

Goldsmith AA, Dowson D, Isaac GH, Lancaster JG: A comparative joint simulator study of the wear of metal-on-metal and alternative material combinations in hip replacements. *Proc Isnt Mech Eng* 214(1):39-47, 2000.

Green AS, O'Connell MK, Lyons AS, James SP: The design and development of a triaxial wear-testing joint simulator. *Biomed Sci Instrum* 35:379-384, 1999.

Jazrawi Lm, Bogner E, Della Valle CJ, et. al.: Wear rates of ceramic-on-ceramic bearing surfaces in total hip implants: a 12-year follow-up study. *J Arthroplasty* 14(7):781-787, 1999.

Kaddick C, Wimmer MA: Hip simulator wear testing according to the newly introduced standard ISO 14242. *Proc Inst Mech Eng* 215(5):429-442, 2001.

McKellop H, Shen FW, Lu B, Campbell P, Salovey R: Effect of sterilization method and other modifications on the wear resistance of acetabular cups made of ultra-high molecular weight polyethylene. A hip-simulator study. *J Bone Joint Surg Am* 82-A(12):1708-1725, 2000.

Miller MC, Zhang AX, Petrella AJ, Berger RA, Rubash HE: The effect of component placement on knee kinetics after arthroplasty with an unconstrained prosthesis. *J Orthop Res* 19(4):614-620, 2001.

Improved Imaging Techniques

Asano T, Akagi M, Tanaka K, Tamura J, Nakamura T: In vivo three-dimensional knee kinematics using a biplanar image matching technique. *Clin Orthop* 388:157-166, 2001.

Conrozier T, Lequesne M, Favret H, et. al.: Measurement of the radiological hip joint space width. An evaluation of various methods of measurement. *Osteoarthritis Cartilage* 9(3):281-286, 2001.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Hide IG, Grainger AJ, Wallace IW, Hui A, Campbell RS: A radiological technique for the assessment of wear in prosthetic knee replacements. *Skltal Radiol* 29(10):583-586, 2000.

Moorehead JD, Harvey DM, Montgomery SC: A surface-marker imaging system to measure a moving knee's rotational axis pathway in the sagittal plane. *IEEE Tans Biomed Eng* 48(3):384-393, 2001.

Sychterz CJ, Young AM, Engh CA: Effect of radiographic quality on computer-assisted head penetration measurements. *Clin Orthop* May(386):150-158, 2001.

Kinematic Analysis

Hartford JM, Banit D, Hall K, Kaufer H: Radiographic analysis of low contact stress meniscal bearing total knee replacements. *J Bone Joint Surg Am* 83-A(2):229-234, 2001.

Hoff WA, Komistek RD, Dennis DA, Gabriel SM, Walker SA: Three-dimensional determination of femoral-tibial contact positions under in vivo conditions using fluoroscopy. *Clin Biomech* 13(7):455-472, 1998.

Stiehl JB, Komistek R, Dennis DA: A novel approach to knee kinematics. *Am J Orthop* 30(4):287-293, 2001.

Stiehl JB, Komistek RD, Dennis DA, Keblish PA: Kinematics of the patellofemoral joint in total knee arthroplasty. *J Arthroplasty* 16(6):706-714, 2001.

Wada M, Tatsuo H, Kawahara H, Sato M, Baba H: In vivo kinematic analysis of total knee arthroplasty with four different polyethylene designs. *Artif Organs* 25(1):22-28, 2001.

Navigation

Gebhard F, Arand M, Fleiter T, et. al.: Computer-assisted surgery: developments and prospects in 2001. Results of a workshop at Schloss Reisenburg, 23-24 November 2000. *Unfallchirurg* 104(8):782-788, 2001.

Handels H, Ehrhardt J, Plotz W, Poppl SJ: Three-dimensional planning and simulation of hip operations and computer-assisted construction of endoprostheses in bone tumor surgery. *Comput Aided Surg* 6(2):65-76, 2001.

Jenny JY, Boeri C: Navigated implantation of total knee endoprostheses—a comparative study with conventional instrumentation. *Z Orthop Ihre Grenzgeb* 139(2):117-119, 2001.

Mielke RK, Clemens U, Jens JH, Kershally S: Navigation in knee endoprosthesis implantation—preliminary experiences and prospective comparative study with conventional implantation technique. *Z Orthop Ihre Grenzgeb* 139(2):109-116, 2001.

Sati M, de Guise JA, Drouin G: Computer assisted knee surgery: diagnostics and planning of knee surgery. *Comput Aided Surg* 2(2):108-123, 1997.

Wagner A, Undt G, Watzinger F, et. al.: Principles of computer-assisted arthroscopy of the temporomandibular joint with optoelectronic tracking technology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 92(1):30-37, 2001.

Other Joints

Haugstvedt JR, Berglund LJ, Neale PG, Berger RA: A dynamic simulator to evaluate distal radio-ulnar joint kinematics. *J Biomech* 34(3):335-339, 2001.

Joyce TJ, Unsworth A: The design of a finger wear simulator and preliminary results. *Proc Inst Mech Eng* 214(5):519-526, 2000.

Meyer C, Kahn JL, Lambert A, Boutemy P, Wilk A: Development of static simulator of the mandible. *J Craniomaxillofac Surg* 28(5):278-286, 2000.

Schwarz ML, Bouman HW, Bayer M, Feinle P: Design and construction of a simulator for testing finger joint replacements. *Biomed Tech (Berl)* 46(6):176-180, 2001.

DEXA

Cohen B, Rushton N: Bone remodeling in the proximal femur after Charnely total hip arthroplasty. *J Bone Joint Surg Br* 77(5):815-819, 1995.

Kerner J, Huiskes R, van Lenthe GH, et. al.: Correlation between pre-operative periprosthetic bone density and post-operative bone loss in THA can be explained by strain-adaptive remodeling. *J Biomech* 32(7):695-703, 1999.

Korovessis P, Droutsas P, Piperos G, et. al.: Course of bone mineral content changes around cementless Zweymueller total hip arthroplasty. A 4-year follow-up study. *Arch Orthop Trauma Surg* 116(1-2):60-65, 1997.

Kruger A, Berli B, Lampert C, Kranzlin C, Morscher E: Comparative periprosthetic bone density measurements of the proximal femur shaft using dual energy x-ray absorptiometry (DEXA) with experimental "Press Fi-gliding Stem Prosthesis". *Z Orthop Ihre Grenzgeb* 136(2):115-125, 1998.

Martini F, Kremling E, Schmidt B, Sell S, Mayer F: Bone mineral density of the proximal femur after unilateral cementless total hip replacement. *Int Orthop* 23(2):104-106, 1999.

Reiter A, Sabo D, Simank HG, et. al.: Periprosthetic mineral density in cement-free hip replacement arthroplasty. *Z Orthop Ihre Grenzgeb* 135(6):499-504, 1997.

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

Sabo D, Reiter A, Simank HG, et. al.: Periprosthetic mineralization around cementless total hip endoprosthesis: longitudinal study and cross-sectional study on titanium threaded acetabular cup and cementless Spotorno stem with DEXA. *Calcif Tissue Int* 62(2):177-182, 1998.

RSA

Alfaro-Adrian J, Gills HS, Marks BE, Murray DW: Mid-term migration of a cemented total hip replacement assessed by radiostereometric analysis. *Int Orthop* 23(3):140-144, 1999.

Fleming BC, Peura GD, Abate JA, Beynnon BD: Accuracy and repeatability of Roentgen stereophotogrammetric analysis (RSA) for measuring knee laxity in longitudinal studies. *J Biomech* 34(10):1355-1359, 2001.

Hilding MB, Lanshammar H, Ryd L: Knee joint loading and tibial component loosening. RSA and gait analysis in 45 osteoarthritic patients before and after TKA. *J Bone Joint Surg Br* 78(1):66-73, 1996.

Hilding MB, Yuan X, Ryd L: The stability of three different cementless tibial components. A randomized radiostereometric study in 45 knee arthroplasty patients. *Acta Orthop Scand* 66(1):21-27, 1995.

Nivbrant B, Karrholm J, Soderlund P: Increased migration of the SHP prosthesis: radiostereometric comparison with the Lubinus SP2 design in 40 cases. *Acta Orthop Scand* 70(6):569-577, 1999.

Ostgaard SE, Gottlieb L, Toksvig-Larsen S, et. al.: Roentgen stereophotogrammetric analysis using computer-based image-analysis. *J Biomech* 30(9):993-995, 1997.

Regner L, Carlsson L, Karrholm J, Herberts P: Tibial component fixation in porous-and hydroxyapatite-coated total knee arthroplasty: a radiostereometric evaluation of migration and inducible displacement after 5 years. *J Arthroplasty* 15(6):681-689, 2000.

Uvehammer J: Knee joint kinematics, fixation and function related to joint area design in total knee arthroplasty. *Acta Orthop Scand Suppl* 72(299):1-52, 2001.

Uvehammer J, Regner L, Karrholm J: Flat vs. concave tibial joint surface in total knee arthroplasty: randomized evaluation of 39 cases using radiostereometry. *Acta Orthop Scand* 72(3):257-265, 2001.

Walker PS, Sathasivam S: A simplified radiographic method for measuring bone-component motion in total knees. *J Biomech* 25(9):1059-1066, 1992.

V. PANEL MEMBERS

Chair:	Bernard Stulberg, MD	Cleveland Center for Joint Reconstruction	Cleveland, OH
Co-chair:	Josh Jacobs, MD	Rush Presbyterian St. Lukes Med Ctr	Chicago, IL
	Mathias Bostrom, MD	Hospital for Special Surgery	New York, NY
	Thomas Brown, PhD	Univ of Iowa	Iowa City, IA
	Dwight Davy, PhD	Case Western Reserve University	Cleveland, OH
	Jeremy L. Gilbert, PhD	Syracuse University	Syracuse, NY
	Stuart Goodman, MD	Stanford Univ Medical Ctr	Stanford, CA
	A. Seth Greenwald,	Orthopaedic Research Lab	Cleveland, OH
	Cato Laurencin, PhD, MD	University of Virginia	Charlottesville, VA
	Jack Lemons, PhD	Univ of Alabama	Birmingham, AL
	Harry McKellop, PhD	Univ of California, Los Angeles	Los Angeles, CA
	Lutz-Peter Nolte, PhD	University of Bern	Bern, Switzerland
	Clare Rimnac, PhD	Case Western Reserve University	Cleveland, OH
	Harry Skinner, MD	Univ of California, Irvine	Orange, CA
	William Tomford, MD	Massachusetts General Hospital	Boston, MA
	King Yang, PhD	Wayne State University	Detroit, MI

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel XVI: Joint Replacement

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Replacement of painful, damaged joints is one of the most significant developments in the treatment of arthritis. Over 500,000 total joint replacements are performed each year in the United States with the vast majority being successful and resulting in substantial functional improvement for the patients. Improvement in function, in turn, permits patients to maintain independent, productive lives and reduces dependency upon institutions, family, and social services.

Areas of research are designed to improve effectiveness of joint replacements and reduce complications and can be grouped into three general categories: implant design, including biomaterials, kinematics, and fixation to bone; measurements of outcome; and identification and treatment of complications including loosening and osteolysis, and technical and medical complications.

B. *Importance to Public Health*
Joint replacement of the hip and knee are among the most successful procedures for improving the quality of life among patients in chronic pain. The earliest attempts at joint replacement (knee) were made more than 100 years ago, while the first hip replacement was made in 1923. Since that time, the procedure has improved dramatically, with success rates of 10 or more years commonly reported for both hip and knee. In 1999, the National Hospital Discharge Survey (NHDS) reported 168,106 total hip replacement procedures were conduced, while 267,103 total knee replacement procedures were recorded in the United States alone. This is an increase of 22% for hip and 9% for knee replacements in a just a four year period, based on NHDS data from 1996. Staff at the American Academy of Orthopaedic Surgeons, utilizing trend lines based on average increase over this four year period, project that by the year 2030, total hip and knee replacement procedures will have grown by 62% and 71%, respectively, with an expected 272,200 hip and 457,500 knee replacements occurring. In addition to hip and knee replacements, joints in the fingers, shoulder, and toes are also common replacement sites, particularly as a result of osteoarthritis. Although alternative treatments for osteoarthritis are being explored that could reduce the need for joint replacements, reducing the current racial and geographical disparities in the delivery of joint replacement procedures will likely increase the volume of joint replacements being performed annually.

II. RECENT ADVANCES

A. *Biomaterials*
Recent studies have identified wear-generated polyethylene debris as the major cause of implant failure. Alternative bearing surfaces including cross-linked polyethylene, ceramics, and metal-on-metal devices have been developed to address problems related to implant wear.

B. *Implant Design and Kinematics*
To what extent do, or should, joint replacements mimic normal kinematics remains a topic of lively discussion. This is particularly true in knee arthroplasty where recent kinematic advances have explored changing centers of rotation with implications for extensor mechanism strength and the role of cruciate substitution or preservation. New interests in unicompartmental knee arthroplasties permit retention of bone and ligaments and, possibly, more normal kinematics. Femoral head resurfacing has been reintroduced which may perhaps permit more normal kinematics and force transmission to bone in hip replacements.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

C. *Implant Fixation to Bone*
Polymethylmethacrylate is no longer seen as the major cause of implant failure and pressurized cement techniques are now acceptable components of implant fixation, especially in knee arthroplasties. Exploration of biological fixation methods has continued. Hydroxyapatite coatings in hip replacements have been show to be useful, primarily in young patients. Porous and textured metal technologies have been shown to be reliable methods of fixation for the acetabular component, and for the femoral stem for both proximal and fully coated applications.

D. *Septic Loosening and Osteolysis*
Osteolysis and implant loosening have been shown to be accompanied by an inflammatory response with osteoclastic bone resorption induced by wear particles of polyethylene. A number of pharmacological attempts have been made to reduce osteoclastic bone resorption, especially second and third generation bisphosphonates.

E. *Measurements of Outcome*
A number of measurement instruments have recently been validated for the description of joint specific and quality of life outcomes after total joint arthroplasty. These and other techniques have been used to demonstrate the favorable impact of total joint replacement on individuals and communities. In fact, previous data on large area variation in joint replacement utilization have been restudied and reinterpreted to suggest that variations in frequency of joint replacements may be due to under-, rather than over-, utilization.

F. *Technical Complications*
The commonest technical complication after total hip replacement is dislocation, occurring in 10% in many series. Recent advances in biomaterials including cross- linked polyethylene, ceramics, and metal on metal articulations have permitted the use of larger diameter femoral heads. This innovation, together with increasing the offset of femoral implants have, in some studies, reduced the incidence of dislocation. Newer techniques of muscle repair may be useful as well. Arthrofibrosis is a significant complication after total knee replacement resulting in loss of range of motion and pain. The cause of arthrofibrosis is not known and there are currently no techniques for prevention. Some successes have been achieved with arthroscopic debridement after knee replacement increasing range of motion.

G. *Medical Complications*
1. Infections after total joint replacement remain a devastating complication and occur in approximately 1% of arthroplasties. They may be difficult to diagnose and characterize. Recent advances have included identification of bacteria with molecular techniques including RT-PCR.
2. The incidence of deep venous thrombosis (DVT) has largely been brought under control with the routine usage of anticoagulants such as warfarin. Efforts to introduce a number of heparin formulations have been successful and are under evaluation as alternative strategies for the reduction of thrombosis and embolism. The efficacy of combined approaches to reduce the likelihood of bleeding complications while reducing the rate of DVT, including the use of salicylates and pneumatic compression devices have also been demonstrated.

III. FUTURE DIRECTIONS OF RESEARCH

A. *Biomaterials*: investigate the short and long term outcomes of
1. Ceramic-on-polyethylene surfaces
2. Hard-bearing surfaces including ceramic-on-ceramic and metal-on-metal

B. *Implant Design and Kinematics*
1. Joint replacement in the young, active patient
2. Computer modeling

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

3. Extensor mechanism problems in total knee replacement

C. *Implant Needs*
   1. Develop and better understand the use of bone graft substitutes to manage osseous defects
   2. Fixation to Bone
      a. Prosthetic surfaces and coatings
      b. Growth factors

D. *Aseptic Loosening and Osteolysis*
   1. Reduce the formation of polyethylene wear and debris
   2. Better understand and reduce the biological response to particulate debris, especially with polyethylene

E. *Technical Complications*: approaches to end
   1. Dislocation in total hip replacement
   2. Arthrofibrosis in total knee replacement

F. *Medical Complications*
   1. Infection, venous thrombosis and pulmonary embolism
   2. Blood Utilization

G. *Newer Joints*: For all these joints, long-term results with functional outcomes and revision surgery rates need to be reported.
   1. Ankle
   2. 1st Metatarsal - phalangeal
   3. Thumb CMC joint
   4. Wrist

H. *Impact of New Surgical Approaches*
   1. The impact of small incision, minimally invasive surgical approaches on functional outcomes, complications, and revision rates needs to be reported in controlled trials.
   2. The impact of robotic assisted surgery on the same measures also needs to be studied in control trials.

IV. SELECTED REFERENCES

American Academy of Orthopaedic Surgeons. "Improving Musculoskeletal Care in America (IMCA) Information Series: Osteoarthritis of the Knee. 2002.

American Academy of Orthopaedic Surgeons. "Primary total hip and total knee arthroplasty projections to 2030". 2003.

National Center for Health Statistics. National Hospital Discharge Survey (NHDS). 1996-1999.

Weinstein, J. *The Dartmouth Atlas of Musculoskeletal Health Care*. Chicago, IL: AHA Press; 2000.

V. PANEL MEMBERS

Chair:	Roy Aaron MD	Brown University	Providence, RI
Co-chair:	John Callaghan MD	Univ of Iowa	Iowa City, IA
	Michael Keating, MD	Center for Hip and Knee Surgery	Mooresville, IN
	Wesley Mesko, MD	Ingham Regional Med Ctr.	Lansing, MI
	Giles Scuderi, MD	Insall Scott Kelly Institute	New York, NY
	James Stiehl, MD	Medical College of Wisconsin	Milwaukee, WI
	Alfred Tria, MD	Medical Center at Princeton	Princeton, NJ
	Kelly Vince, MD	Univ of Southern California	Los Angeles, CA
	Tim Wright, PhD	Hospital for Special Surgery	New York, NY

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

(blank page for correct printing)

Panel XVII: Workplace Injuries and Ergonomics

I. DESCRIPTION OF SCOPE

A. *Clinical Significance*
Musculoskeletal injuries related to the workplace are among the most costly health problems facing society today. In 1999, almost 1 million people took time away from work to be treated and to recover from work-related musculoskeletal pain or impairment of function. The economic burden of these musculoskeletal problems is conservatively estimated at between $45 billion and $53 billon annually. Currently, the low back and the upper extremity are the parts of the body most subject to risk associated with work. The literature recognizes that this risk arises from many simultaneously contributing factors. Individual factors, such as workplace physical requirements, organizational factors, and psychosocial factors have been associated with this risk. Epidemiological studies have shown that between 11% and 80% of low back injuries and 11% to 95% of extremity injuries are attributable to workplace physical factors. Between 14% and 63% of injuries to the low back and between 28% and 84% of injuries of the upper extremity are attributable to psychosocial factors.

The importance of ergonomics to orthopaedic surgery lies in its potential to prevent primary musculoskeletal disorders attributable to work, as well as in its potential to minimize the risk of re-injury or secondary injury when returning to the workplace. The goal of ergonomic science is to understand the causality of work-related musculoskeletal disorders and use this knowledge to reduce work-related risk. Traditionally, the disciplines of biomechanics, physiology, and psychophysics have dominated the body of knowledge that has defined exposure limitations to work.

B. *Importance to Public Health*
Effective management to reduce the risk of low back and upper extremity injuries in the workplace has been associated with the introduction of ergonomic programs, engineering and administrative controls, and selected employee-oriented modifications. Studies involving these interventions provide a means to assess the impact of ergonomic changes on society. Unfortunately, many of these studies lack the scientific rigor to decisively assess the impact of these interventions on the risk of workplace musculoskeletal injury.

II. RECENT ADVANCES

A. *Exposure Metrics*
Exposure metrics is the ability to quantify the physical characteristics of the environment to which workers are exposed. This field of ergonomics has been applied to the workplace to better quantify low back disorder risk. Objectively measuring the nature of the physical load involved in a given work task, the degree of the repetition required to performing a certain task, as well as the kinematics (movements) and time needed to accomplish a specific task have improved our ability to define “overexposure” for a given work condition.

B. *Spine Lifting Loads*
During actual lifting tasks, the ability to estimate the three-dimensional loads imposed on the spine has improved significantly with the development of biologically assisted engineering mechanical models and static and dynamic stability models of the spine.

C. *Deterioration Due to Loading Stress*
1. Finite element modeling techniques have enhanced the ability to understand the deterioration process of structures to occupational loading. With such techniques, the ability to specify tolerance limits for the spine has improved significantly. While early

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

studies permitted an assessment only of the static upright positions of the spine, latter efforts have permitted tolerance limits to be defined in response to dynamic conditions of bending, repetition, and asymmetry.

2. Pathomechanics involves the ability to assess musculoskeletal tissue reactions in response to mechanical loading. Improvements in this field have allowed better understanding of the response of tissues to repeated low load level insults. Recent studies have shown how repetitive motions or overuse loading can result in chronic injury to tendon tissues. The biochemical responses to such stress are being defined, and the interaction between mechanical load, adaptation, and tolerance are being explored.

D. *Mechanobiology*
The field of mechanobiology, which explores the biological reaction of human tissue to mechanical force, has evolved rapidly. Investigations (involving primarily animal models) have begun to address how repetitive mechanical strain exceeding tolerance limits, imposed in various ways, can result in chronic skeletal muscle injury.

E. *Compression Impact on Nerves*
Tolerance studies of nerves have shown that low-grade compression, in particular of peripheral nerves, may release cytokines and neurotransmitters (substance P, Tumor Necrosis Factor-alpha(TNFα), etc.) that stimulate pain transmission.

F. *Role of Psychosocial Factors in Stress Response*
1. The role of psychosocial factors has been better delineated. Psychosocial factors include nonphysical influences that concern the mental stress response of the worker in the workplace. The risk factors associated with psychosocial factors associated with organizational structures and social contexts have been defined.

2. The pathways by which multidimensional factors might influence spine loading have been initially described. The role of personality factors and psychosocial factors in influencing muscle coactivity and subsequent spine loading has been described.

III. FUTURE DIRECTION OF RESEARCH

A. *Changing Work Stresses from Low-Force, Repetitive Situations*
Traditionally, high-force, highly repetitive loading of the musculoskeletal system has been the hallmark of work. However, the nature of the work and place in which an individual is employed is changing rapidly. Less manufacturing where employees work on a traditional assembly line is being performed. More assembly is occurring in work cells where employees now perform a variety of tasks and may rotate through different work stations throughout the day. Collectively, these trends indicate that the nature of physical exposure is rapidly evolving to a low-force, highly repetitive situation where the repetition may involve different vectors of force application. Research efforts must now examine these new environments with protocols adapted to this new form of musculoskeletal loading.

B. *Role of Risk Factors in Stress Injuries*
All research efforts must be directed towards better quantifying the role of the various risk factors in the mix of exposures common in the workplace. Efforts to quantitatively link epidemiological, loading, tolerance, and psychosocial studies should be pursued so that a better understanding of the pathways of injury and resultant preventive strategies can be assessed.

C. *Furthering Knowledge of Mechanobiology*
While significant advances in the field of mechanobiology have occurred in recent years, further work is needed to clarify the response of tissue to loading and the pain pathways

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262

associated with this relationship. Much of our knowledge about tissue tolerance, especially that related to repetitive loading has been gained from cadaver studies. Such data do not reflect the biological system's ability to temporally adapt to conditions that occur during actual working conditions. Future research efforts must describe this in-vivo tolerance of healthy as well as compromised tissues.

D. *Magnitude and Impact of Shoulder Injuries*
Worldwide trends have shown that shoulder problems are common and are occurring with increased frequency in the workplace. This trend appears to be unrecognized in US industry. Better surveillance is needed to appreciate the magnitude of risk associated with shoulder loading in the workplace. As people live longer, and the average age of the US work force increases, the impact of aging on work-related loading, tolerance, psychosocial stress, and their interactions must be better investigated.

E. *Workplace Factors in Fibromyalgia*
The role of workplace factors in the development of fibromyalgia has been virtually unexplored; yet many symptoms of work-related musculoskeletal disorders resemble myofacial pain. Research efforts must focus on how low-level sustained or repetitive exertions may influence muscle recruitment patterns and possibly lead to fibromyalgia.

F. *Early Return-to-Work Risks*
Research involving risk of secondary injury associated with return-to-work is sparse. Epidemiological, tissue loading, pathomechanics tolerance, and psychosocial studies are needed to determine and describe how risk is affected when an individual is exposed to work while recovering from a musculoskeletal disorder.

G. *Continued Understanding of Causality and Role of Intervention in Workplace Injuries*
A continuing need exists for high-quality intervention studies. Most research has focused on the causal relationship between work and musculoskeletal disorders. However, the effectiveness of intervening in this relationship can be established only through high quality intervention studies. Studies must overcome the traditional limitations in these efforts to better establish causality and effectiveness of interventions.

IV. REFERENCES

Adams MA, Freeman BJ, et al: Mechanical initiation of intervertebral disc degeneration. *Spine* 2000;25(13):1625-1636.

Andersson GB: The epidemiology of spinal disorders, in J. W. Frymoyer (ed): *The Adult Spine: Principles and Practice*. Philadelphia, PA, Lippincott-Raven, 1997, 1: 93-141.

Bigos SJ, Battie MC, et al: A prospective study of work perceptions and psychosocial factors affecting the report of back injury [published erratum appears in Spine 1991 Jun;16(6):688]. *Spine* 1991;16(1):1-6.

Bongers PM: The cost of shoulder pain at work. *BMJ* 2001;322(7278): 64-65.

Burdorf A, Sorock G: Positive and negative evidence of risk factors for back disorders. *Scand J Work Environ Health* 1997;23(4): 243-256.

Callaghan JP, Salewytsch AJ, et al: An evaluation of predictive methods for estimating cumulative spinal loading. *Ergonomics* 2001;44(9): 825-837.

Cavanaugh JM, Ozaktay AC, et al: Mechanisms of low back pain: A neurophysiologic and neuroanatomic study. *Clin Orthop* 1997;(335): 166-180.

Dasinger LK, Krause N, et al: Physical workplace factors and return to work after compensated low back injury: A disability phase-specific analysis. *J Occup Environ Med* 2000;42(3): 323-333.

Dennerlein JT, Diao E, et al: In vivo finger flexor tendon force while tapping on a key switch. *J Orthop Res* 1999;17(2): 178-184.

Deyo RA, Bass JE: Lifestyle and low-back pain: The influence of smoking and obesity." *Spine* 1989 ;14(5): 501-506.

Deyo RA, Battie M, et al: Outcome measures for low back pain research. A proposal for standardized use." *Spine* 1998;23(18): 2003-2013.

Copyright © American Academy of Orthopaedic Surgeons

6300 North River Road, Rosemont, IL 60018-4262

Fathallah, FA, Marras WS, et al. (1998). “The role of complex, simultaneous trunk motions in the risk of occupation-related low back disorders.” Spine 23(9): 1035-42.

Ferguson SA, Marras WS: A literature review of low back disorder surveillance measures and risk factors. *Clinical Biomechanics* 1997;12: 211-226.

Frank JW, Kerr MS, et al: Disability resulting from occupational low back pain. Part I: What do we know about primary prevention? A review of the scientific evidence on prevention before disability begins. *Spine* 1996;21(24): 2908-2917.

Granata KP, Marras, WS: An EMG-assisted model of trunk loading during free-dynamic lifting. *J Biomech* 1995;28(11): 1309-1317.

Hoogendoorn WE, van Poppel MN, et al: Systematic review of psychosocial factors at work and private life as risk factors for back pain. *Spine* 2000;25(16): 2114-2125.

Hutton WC, Ganey TM, et al: Does long-term compressive loading on the intervertebral disc cause degeneration? *Spine* 2000;25(23): 2993-3004.

Karjalainen K, Malmivaara A, et al: Multidisciplinary biopsychosocial rehabilitation for subacute low back pain in working-age adults: A systematic review within the framework of the Cochrane collaboration back review group. *Spine* 2001;26(3): 262-269.

Lavender SA, Oleske DM, et al: Comparison of five methods used to determine low back disorder risk in a manufacturing environment. *Spine* 1999;24(14): 1441-1448.

Liles DH, Deivanayagam S, et al: A job severity index for the evaluation and control of lifting injury. *Hum Factors* 1984;26(6): 683-693.

Lotz JC, Chin JR: Intervertebral disc cell death is dependent on the magnitude and duration of spinal loading.” *Spine* 2000;25(12): 1477-1483.

Marras WS, Davis KG, et al: Spine loading characteristics of patients with low back pain compared with asymptomatic individuals. *Spine* 2001;26(23): 2566-74.

Marras WS, Davis KG, et al: The influence of psychosocial stress, gender, and personality on mechanical loading of the lumbar spine.” *Spine* 2000;25(23): 3045-3054.

McGill SM: The biomechanics of low back injury: implications on current practice in industry and the clinic. *J Biomech* 1997; 30(5): 465-475.

Norman R, Wells R, et al: A comparison of peak vs cumulative physical work exposure risk factors for the reporting of low back pain in the automotive industry. *Clinical Biomechanics* 1998;13: 561-573.

(NRC), N. R. C. Work-related musculoskeletal disorders: report, workshop summary, and workshop papers. Washington D.C., National Academy Press. 1999.

(NRC), N. R. C. Musculoskeletal disorders and the workplace: low back and upper extremity. Washington D.C., National Academy Press. 2001.

Oleske DM, Andersson GB, et al: Association between recovery outcomes for work-related low back disorders and personal, family, and work factors.” *Spine* 2000;25(10): 1259-1265.

Punnett L, Fine LJ, et al: Shoulder disorders and postural stress in automobile assembly work [In Process Citation]. *Scand J Work Environ Health* 2000;26(4): 283-291.

Rempel DM, Harrison RJ, et al: Work-related cumulative trauma disorders of the upper extremity. *JAMA* 1992;267(6): 838-842.

Solomonow M, Zhou BH, et al: Biomechanics of increased exposure to lumbar injury caused by cyclic loading: Part 1. Loss of reflexive muscular stabilization. *Spine* 1999;24(23): 2426-2434.

Vasseljen O, Holte KA, et al: Shoulder and neck complaints in customer relations: Individual risk factors and perceived exposures at work. *Ergonomics* 2001;44(4): 355-372.

Viikari-Juntura E, and Silverstein B: Role of physical load factors in carpal tunnel syndrome. *Scand J Work Environ Health* 1999;25(3):163-185.

Waddell G: Biopsychosocial analysis of low back pain. *Baillieres Clin Rheumatol* 1992;6(3): 523-557.

Westgaard RH, Winkel J: Ergonomic intervention research for improved musculoskeletal health: A critical review. *International Journal of Industrial Ergonomics* 1997;20: 463-500.

V. PANEL MEMBERS

Chair:	Sheldon Simon, MD	Beth Israel Medical Center	New York, NY
Co-chair:	William Marras, PhD	Ohio State University	Columbus, OH
	Purnendu Gupta, MD	Univ of Chicago	Chicago, IL
	David Rempel, MD	Univ of California, San Francisco	Richmond, CA

Copyright © American Academy of Orthopaedic Surgeons
6300 North River Road, Rosemont, IL 60018-4262