Musculoskeletal Disorders and Orthopedic Conditions

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The Scope of the Problem

The United Nations has declared the years 2000-2010 the “Bone and Joint Decade” to draw attention to the increasing impact orthopedic conditions will have on world health as life expectancy increases and to the potential for eliminating these problems through current and future research advances. A survey by the American Academy of Orthopaedic Surgeons reported that 3 million musculoskeletal and orthopedic procedures were performed in US hospitals in 1995, including those for fractures (15%), joint problems (22%), and spinal disorders (12%). An additional 4.3 million musculoskeletal procedures were performed in outpatient settings.

Musculoskeletal disorders, of which osteoarthritis and back pain are most common, cost approximately $215 billion each year in health care costs and loss of economic productivity.2 Trauma and congenital abnormalities dominate in children and adolescents, whereas in ages 18 through 44 years hospitalizations are mainly for back disorders and knee or other joint problems. In those aged 45 through 65 years, osteoarthritis and spondylitis increase in frequency. Fractures cause more hospitalizations in those aged 65 years and older, accounting for 62% of all musculoskeletal-related hospitalizations in those older than 85 years. Osteoporosis-associated fractures alone are estimated to have cost $14 billion in 1995. However, improvements in diagnostic modalities, imaging techniques, therapeutics, and orthopedic devices will alter these patterns.

Ongoing advances in orthopedics include discoveries of functions of matrix proteins, development of new implant materials that are more durable and more compatible with magnetic resonance imaging, and identification of genes causing musculoskeletal disorders and disease. The Human Genome Project will further clarify the genetic basis of specific musculoskeletal disorders, enhancing risk factor identification, diagnosis, and therapy. Engineered, cell-based materials will replace metals and plastics in implants, and new composite materials will promote bone in-growth.

Major Advances in the Past 25 Years

Between 1975 and 2000, advances in cell and molecular biology as well as advances in design and materials revolutionized orthopedic science. These advances, coupled with those in surgery and health care delivery, changed practice patterns drastically.

The course of progress can be illustrated by total joint arthroplasty. Designs for hip, knee, shoulder, and other joint replacements increased in numbers beginning in the 1960s but over time infection, device breakage, loosening, wear, and wear-debris-induced bone resorption (osteolysis) became apparent, and with these, the need for revision.

Infection has largely been controlled through improved surgical and aseptic techniques and prophylactic antibiotics, but infections remain a serious (and costly) problem for affected individuals. Device breakage has been all but eliminated through new implant design. Aseptic loosening has been reduced through improved surgical techniques. Wear of plastic parts continues to be a problem, although recent development of low-wear materials promises to minimize this problem.

Newer implant materials (eg, titanium and titanium alloys) reduce artifacts associated with magnetic resonance imaging of other metallic materials, facilitating monitoring. The biology of debris-induced osteolysis is being investigated, and current therapies reduce bone resorption and the risk of implant failure.

A second illustration of the basic science revolution in orthopedic surgery comes from the use of mouse models to facilitate identification of genes that cause musculoskeletal deformities and disease. In addition to accelerating gene identification, mice with altered genes provide models for evaluating therapeutics and new clues into the origin of developmental abnormalities. Gene identification and proteomics (the study of protein function) are increasing at an exponential rate. While in the past 25 years the emphasis was on developing techniques for protein isolation, gene sequencing, and cloning in the last few years the emphasis has...
Basic Science Discoveries Translated to Orthopedic Interventions

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turned to determining the function of these proteins⁴⁰ and to the development of novel interventions.

Current Scientific Foundation

The Human Genome Project⁴⁹ will markedly clarify the genetic basis of specific musculoskeletal diseases, and emerging technology will soon allow predictive genes to be identified prior to disease presentation. The major advances will come in functional genomics, as the functions of musculoskeletal genes are elucidated.⁵⁰ “Gene chips” may soon be available to provide specific genetic information on musculoskeletal diseases. These high-density arrays of oligonucleotides (currently available with thousands of known gene sequences) can rapidly detect the presence of normal and modified genes in a serum extract.⁵⁰ The 21st-century orthopedic surgeon will likely determine if a patient with a fracture has any mutation regulating cell proliferation, matrix protein production, or other factors placing him or her at risk for nonunion. Similarly, surgeons will be able to review genetic analyses and select therapeutic modalities based on factors for rapid (or slow) degeneration of cartilage, osteoporosis, or other bone, joint, and muscle diseases.

In the last few years, master genes controlling the development of bone and cartilage have been identified,⁵¹-⁵⁴ and new drug discovery, intimately coupled to molecular understanding,⁵⁷ is revolutionizing orthopedic practice. Evolving pharmaceuticals provide highly targeted (specific) drugs that affect specific biochemical pathways, rather than multiple pathways in which drugs have unintended effects.⁵⁵ These advances have been made possible by studies of cell behavior and facilitated by studies of biochemical pathways at the level of genes and proteins.⁵⁶ Even more specific drugs will emerge in the future. To illustrate, in 1998 a protein that controls differentiation and activation of bone resorbing osteoclasts (osteoprotegerin ligand) was identified, cloned, and synthesized; soluble antagonists were then developed and are being evaluated in clinical trials to prevent bone loss.⁵⁷ The speed of drug discovery will have to be met by development of mechanisms for targeted delivery of the drug only to the tissue or cells of interest. The combination of cellular, molecular, and diagnostic techniques together with newly developed analysis systems for processing this information will provide an opportunity for rapid clinical advances. These approaches will be particularly applicable to congenital, developmental, and degenerative conditions.

In addition to knowledge of the molecular bases of musculoskeletal diseases, orthopedic devices have also benefited from a combination of bioengineering, chemistry, cell biology, genetics, and medicine (ie, “tissue engineering”) that has led to new technologies entering the clinical arena.⁵⁷-⁶² Sophisticated computer science has also led to the development of surgical robotic tools.⁶² Complementing basic research are newly emerging approaches to assessing the short- and long-term outcomes

620 JAMA, February 7, 2001—Vol 285, No. 5 (Reprinted) ©2001 American Medical Association. All rights reserved.
of orthopedic interventions. These approaches provide objective means to determine the impact of treatments on the quality of life of individuals, as well as the economic impact on society. In this period of “evidence-based medicine,” it is now practical to determine whether new treatments achieve their purpose.

Cutting-Edge Research Activities

A number of new tools and approaches are likely to lead to changes in the practice of orthopedics during the next 25 years. Innovative diagnostic techniques will enable surgeons to obtain detailed information on the quality of musculoskeletal tissues at the microscopic level, thus affording earlier opportunities for identification of problems and intervention, and for monitoring the effects of interventions. Image analysis, 3-dimensional reconstruction, and telemetry will provide this information in formats viewable in the operating room. Functional genomics will facilitate early diagnosis, allowing early prophylactic actions. Although to date orthopedic gene therapy has been limited to animal models, clinical trials for treatment of arthritis are currently in progress. Once the identities of the genes contributing to the disease are known, and the proteins resulting from expression of such genes identified and the delivery systems developed, gene therapy is likely to become more widespread.

While tissue engineering in a general sense has been available for decades, composite materials mimicking bone and cartilage have only recently become available for clinical use. Current research is focused on improving the carriers and selecting cells for incorporation into these composites. Tissue engineers will need to determine what signals organize the matrix produced by cells in the composites (FIGURE). Nanotechnology allows the structure and function of body tissues to be mimicked in the laboratory, and these fabricated materials may soon become available for clinical use. Based on current progress it is likely that, in the near future, the use of metals or plastics will be limited: instead, patients will receive cell-based materials. For large bone defects, these composites will have to have mechanical integrity, but they will be more biologically based.

Based on existing studies and outcomes analysis it is likely that future implants will last longer with less risk of wear or loosening. While this implies fewer revisions, wider use in young individuals may offset some gains while increasing overall quality of life. With increased knowledge of factors controlling bone development and cell differentiation, composite materials will be fashioned that facilitate ingrowth.

Forecast of Research Advances

Orthopedic surgery in 2025 will be very different from what it is today. Current basic science research (eg, genomics, proteomics, tissue engineering, computational chemistry for drug discovery and delivery, and nanotechnology for new materials) will lead to new diagnostic procedures, better prophylactic techniques, earlier interventions, and new materials for repair. Critical elements will include education of clinicians and patients and development of techniques for archiving the vast amounts of data to be generated. The theme will be the same for each of the orthopedic subspecialties (total joints, spine, metabolic bone disease, tumors, and trauma): prevention, early intervention, more focused and effective therapies, and longer-lasting repairs. The orthopedic surgeon will not be out of business, but the approach will be different. Because people are living longer, orthopedic operative...
**Research Opportunities and Forecast: Musculoskeletal Disorders and Orthopedics**

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<td>Determine the Genes and Proteins Required for Bone and Cartilage Development and Maturation</td>
<td>Early Diagnosis and Prevention of Congenital Deformities</td>
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<td>Targeted Therapies for Osteoporosis, Osteoarthritis, and Other Musculoskeletal Abnormalities</td>
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<td>Treatment for Genetic Diseases of Bone, Cartilage, Ligament, and Tendon</td>
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<td>Discover the Genetic Bases of Complex Musculoskeletal Diseases</td>
<td>Gene and/or Targeted Protein Therapy for Treatment</td>
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<td>Develop Methodologies to Control the Proliferation, Phenotype Expression, and Transplantation of Musculoskeletal Progenitor Cells</td>
<td>Cell Transplantation for Repair of Musculoskeletal Injuries</td>
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<td>Cell Transplantation for Repair of Damaged Tissues</td>
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<td>Use of Cells for Targeted Gene Therapy</td>
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<td>Establish Methodologies to Engineer Bone, Cartilage, Ligament, Disk, and Tendon</td>
<td>Long-Lasting Biologic Repair of Diseased and Damaged Tissue</td>
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<td>Reliable Substitute for Autologous Bone Grafts</td>
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<td>Develop In Situ Imaging Techniques That Provide Molecular or Cytogenetic Information</td>
<td>Better Selection of Treatment Modalities and Drug Delivery</td>
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practices will probably focus on older individuals, while clinical practice is apt to be focused on diagnosis, prevention, and early intervention in younger individuals. For example, in the case of idiopathic scoliosis, a devastating condition, genetic analyses should facilitate targeted treatment in young children before spinal curvature progresses.

As the emphasis shifts from repair to prevention, surgical practice will focus on trauma, work-related disorders and injuries, and revision of the older devices in use today. The economic impact of musculoskeletal conditions should decrease due to changes and procedures now being developed; for example, in utero correction 

and specific repair techniques developed for sex- and sport-specific injury.

Virtual reality technology will be used for surgical training and long-distance surgery. Various specialties are developing approaches to train surgeons realistically without exposing patients to risk. The US Army and the National Aeronautics and Space Administration are currently evaluating techniques for robotic surgery, with the surgeon at a distant site. Further developments might lead to the performance of relatively simple surgeries or other forms of treatment at remote or rural sites.

Preventive strategies are illustrated by osteoporosis, a complex genetic disease placing some individuals with appropriate diet and exercise histories at high risk for fracture because of genetic factors. Diet, exercise, and fall prevention are currently stressed by the clinician and the media, and many pharmaceutical agents have been developed to reduce bone loss. However, strategies do not yet address the underlying (genetic and molecular) etiologies of the disease. Research must continue to identify the genetic factors that contribute to fracture risk and drugs must be developed to specifically target those factors. A similar set of paradigms should exist for other bone disorders.

Advances based upon burden of disease will nonetheless require effectively translated discoveries and efficiently delivered health care utilizing evidence-based medicine. Basic science discoveries made in the last 25 years have had a major impact on orthopedic practice. The new tools discussed herein are reducing the time required for a discovery to go from bench to bedside. It is critical that the basic science effort continues, that clinical research be expanded, and that the collaboration between the basic scientist and the clinician continues to enable this rapid translation of critical data.

**REFERENCES**

10. Lian JB, Hauschka PV, Gallop PM. Properties and