Aging and the musculoskeletal system

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I heard the old, old men say,
“Everything alters
And one by one we drop away”.
They had hands like claws, and their knees
Were twisted like the old thorn trees
By the waters
W B Yeats

Geriatric and rheumatological linkages: public health implications
Editors in medical journals worldwide have selected aging as the 1997 Global Theme Issue. In proposing this article, the editors of the Annals have considered the importance and implications of the growth of the very elderly population in developed countries and the widespread prevalence of musculoskeletal conditions in this age group. Broadening the scope of this discussion from osteoarthritis, about which I have written in this journal earlier, to include musculoskeletal disorders, permits consideration of a range of interactive conditions that also affect soft tissues, tendons, and ligaments (fibromyalgia, tendinitis), bones (osteoporosis), the intervertebral discs (degeneration), and muscles (polymyalgia, myopathies). This article will focus primarily on aging associated conditions involving bones, muscles, and peripheral joints. Table 1 presents the unifying features of the musculoskeletal disorders. Their public health implications in elderly persons are enormous, and encompass (a) physical and social impacts from pain, limited mobility, reduced quality of life; (b) direct expenditures for diagnosis and treatment; (c) indirect economic costs from loss of participation in the labour force. Among impairments identified in the National Health Interview Survey in 1988, musculoskeletal disorders were the most frequently reported—almost 30 million in the US population. In 1992 the total cost of musculoskeletal and associated conditions for all ages was $149 billion. The elderly incurred the largest share of the direct costs of medical care ($51 billion) with still substantial indirect costs caused by lost wages.

There are at least 26 million white women at risk for fractures by virtue of low bone mass or osteoporosis. Hip fracture incidence will continue to increase—an orthopaedic epidemic—with US expenditures in 1995 estimated at $13.8 billion; fractures at other skeletal sites accounted for 36.9 per cent of health care expenditures nationally and yet have tended to be underestimated. The greater longevity of women compared with men results in older women spending more years living in the disabled state, for which arthritis is by far the most prevalent chronic condition. An estimated 60 per cent of the 65 to 74 year old group in the HANES I study had physician observed musculoskeletal disorders (joint complaints, pain in the back, neck, limited shoulder motion). Several authors emphasise that regional musculoskeletal disorders (for example, tendon lesions, soft tissue rheumatism) have been overlooked in the planning and provision of health care despite their increasing importance. Among elderly persons who have left the work force because of musculoskeletal injuries, 86 per cent of the total costs of such injuries resulted from the direct costs of medical care. In contrast, direct costs accounted for only 39 per cent of the total costs of musculoskeletal conditions not related to injury. Verbrugge and Patrick examined seven chronic conditions and their impact on US adults’ activities and uses of medical services. Arthritis was the most common condition in middle and late life, and the most frequently cited cause of limitations, but had low visibility in biomedical research and health care funding because of ‘low prominence in health services’. The costs to society of musculoskeletal impairments in terms of personal suffering, in limitations of activities, and in health expenditures, should serve as an imperative to health professionals, planners, and legislators, to consider means to promote new research initiatives, foster more extended care services, and encourage preventive strate-
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Prospects for intervention and prevention
The interrelations of aging and components of the musculoskeletal system—muscles, bones, cartilage, soft tissues, tendons—are perhaps best understood in the context of the outcome of muscle strengthening regimens. Trials of exercise interventions seek to define the rationale therapeutic approaches.9

The verse lines of W B Yeats cited above raise geriatric and rheumatological visions of decline and disability, a discouraging note, perhaps appropriate for the outlook almost a century ago. This article aims to project a more positive side for both disciplines based on advances in clinical and basic research that hold out prospects for therapeutic interventions—indeed preventive approaches—that may lead to improved health services and practices to promote a better quality of life for an aging society.

Prospects for early diagnosis and new treatments
Risk factors for osteoarthritis and osteoporosis—the most prevalent conditions of the aging skeleton—are generally well known.27 Newer diagnostic approaches that increase our understanding of the basic mechanisms involved in these conditions and offer the prospects for earlier, potentially remediable therapeutic interventions, are discussed here briefly and with limited references.

BIOCHEMICAL MARKERS OF BONE AND CARTILAGE TURNOVER
Such tests have perhaps come into more widespread use in osteoporosis than in osteoarthritis because of the availability of other correlative studies—such as bone mineral density measurements and analyses of the genetics of the vitamin D receptor (see below). High serum concentrations of osteocalcin and bone specific alkaline phosphatase reflect high bone turnover associated with bone formation, while collagen peptides in urine, particularly bone specific deoxypyridinoline cross links, reflect bone resorption.28 Cartilage and bone markers in osteoarthritis have been studied in relation to radiographic evidence of joint space narrowing, reflecting cartilage loss, and of
subchondral sclerosis and the presence of osteophytes, reflecting bone formation—an 'uncoupling' of the normal balance of degradation and repair in these respective structures. In patients with diagnosed knee osteoarthritis on entry to one study, concentrations of serum hyaluronan and cartilage oligomeric matrix protein were associated with progression at five year follow up. Reduced serum concentrations of vitamin D may be a marker for progression of knee osteoarthritis.

GENETIC ANALYSES
A relation between bone mineral density and polymorphism of the vitamin D receptor gene has been shown in a number of studies, especially on twins, by using restriction enzymes (Bsm1, Apa 1, and Taq 1) on the polymorphic regions. One form of polymorphism in subjects classified as BB (region broken by Bsm1) showed high serum concentrations of osteocalcin and vitamin D and reduced bone density in the femoral neck. However, not all studies have confirmed the prevalence and importance of the genetic association, especially in elderly women age 75 years or more, suggesting that findings may depend on many variables in the study population, including ethnic background, geographical origin, age, pre- or postmenopausal state, calcium intake, and body mass index. A recent meta-analysis of 16 published studies showed a modest effect of vitamin D receptor genotype on bone mineral density at the hip, spine, and radius, with a reduction of about two per cent at these sites in the BB compared with the bb genotype groups. Genetic and environmental factors that contribute to body weight at the age of one year may 'programme' the extent of bone mineral content in the same subjects 60–70 years later, with higher infancy weights projecting a better outcome. A genetic predisposition was observed for osteoarthritis with radiographical findings in the hands and knees in studies on female twin pairs aged 48–69 years.

IMAGING AND DENSITOMETRIC MODALITIES
Advances in the research use of quantitative magnetic resonance imaging make it possible to assess the state of cartilage, joint space width, and bone, in finger joints where changes can be followed up prospectively to distinguish aging from early findings of osteoarthritis, and as a clinical development tool to monitor new drugs affecting matrix turnover and repair. Dual energy x ray absorptiometry has come into widespread clinical use to assess bone density in the femoral neck and spine in subjects at high risk for osteoporosis; however, generalised screening for this condition is not advocated at present.

THERAPEUTIC INTERVENTIONS
The defining lesions in the osteoarthritic joint relate to cartilage fibrillation and loss, and subchondral new bone formation, as noted. The extent of spontaneous healing of cartilage in the early stage of osteoarthritis is uncertain; patients with clinical complaints in the joint who come to arthroscopy may show defects in the cartilage. The use of cells with chondrogenic potential, and growth factors such as transforming growth factor β (TGFβ) or fibroblast growth factors (FGFs) to stimulate cell proliferation and synthesis of matrix components, offer experimental approaches to repair cartilage defects without resorting to surgical debridement. A number of studies have indicated promising results. Infusion of basic type FGF into the joint of a rabbit appeared to repair defects limited to the cartilage, presumably by promoting chondrocyte proliferation and matrix synthesis. Whether these cells have chondrogenic potential is not yet known. When defects are made in cartilage that penetrate into subchondral bone, a different situation prevails: blood vessels and meniscal cells from the marrow enter the blood clot that forms in the cartilage, and chondrogenesis occurs. However, the fibrocartilage that ultimately forms is not stable and deteriorates over time. New therapeutic approaches to increase bone formation in osteoporosis or to repair cartilage defects in osteoarthritis are likely to arise from a greater understanding of the influence of growth factors on these tissues or their progenitor mesenchymal stem cells. Techniques are available for isolating, preserving, and 'directing' the lineage of these stem cells, particularly with the use of components of the TGFβ superfamily, including bone morphogenetic proteins to promote development of osteoblasts, and cartilage derived morphogenetic protein to promote chondrocyte differentiation. The challenge for cartilage repair in vivo will be to stimulate growth of 'articular' chondrocytes and to limit vascular invasion that might lead to endochondral ossification. Increased subchondral bone density in osteoarthritis has attracted much interest as the 'inverse' of bone loss in osteoporosis, yet its mechanisms and ultimate significance are unknown. Sclerosis and stiffness of the cancellous subchondral bone may act biomechanically to promote shearing forces that break down cartilage, although the calcified subchondral plate immediately below the articular cartilage was less stiff in osteoarthritis than normal and thus should absorb energy better. In an aging monkey model spontaneously developing osteoarthritis, dense subchondral bone was found to precede cartilage degeneration. It is not clear at present whether therapeutic options can be developed to 'reduce' subchondral sclerosis and limit osteophyte formation in the knee and hip in osteoarthritis, and even if this were possible, what the long term outcome would be.
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Synovial membrane cells release cytokines, such as interleukin 1 and tumour necrosis factor into the joint cavity, with activation of cyclooxygenase (COX) enzymes that promote chondrocyte production of prostaglandins. COX1 is expressed in a more constant fashion in tissues such as the gastric mucosa, platelets and kidney, while COX2 is augmented in response to cytokines. Until recently, the available NSAIDs generally diminished prostaglandin synthesis by inhibition of COX1, with potent side effects on the kidney and gastric mucosa. As is well known, elderly persons with musculoskeletal complaints are at highest risk for NSAID toxicity yet it is for these people that the drugs are most widely prescribed. NSAIDs with more selective inhibition of COX2 may suppress inflammation in joints with perhaps fewer organ side effects. Disease modifying agents for osteoarthritis would prevent or retard cartilage matrix breakdown and are being explored in animal models. A number of orally active matrix metalloproteinase inhibitors have been tested for specific inhibitory activities against collagenase and stromelysin, and yet difficulties remain in their clinical application. Doxycycline inhibits the activity of collagenase in extracts of articular cartilage, prompting in vivo studies of this potentially disease modifying oral agent in a canine model of osteoarthritis; human clinical trials have also begun. However, as Brandt has noted ‘all the tissues of the involved joint in osteoarthritis are abnormal. We should not dismiss the possibility that pharmacological, biological or physical measures that modify disease processes in subchondral bone, synovium, joint capsule, ligaments, or periarticular muscles will be more effective than a ‘chondroprotective’ drug.’

Age related decline in the secretion of growth hormone, the resulting insulin-like growth factors, and adrenal and gonadal sex steroids, has raised consideration of treatment in subchondral bone, synovium, joint capsule, ligaments, or periarticular muscles will be more effective than a ‘chondroprotective’ drug. The aging of the organism is reflected at the cellular level by the renewal of haematopoietic and mesenchymal stem cells, and by their differentiation and maturation. The derived mature cells (blood cell lineage and osteoclasts, myoblasts, adipose cells, fibroblasts, osteoblasts, and chondroblasts), proliferate, synthesise their characteristic components, and ultimately undergo senescence or follow a path to programmed cell death. These complex cell changes are at all times under genetic control, influenced by growth factors in the environment that arrive via the circulation or are produced by and interactive with the cells. Some stem cells can be instructed to choose one pathway of differentiation by growth factors, while others make this choice in some other predetermined way in which growth factors act as survival factors or mitogens for committed cells. A great deal has been learned recently about the development of osteoblasts and chondrocytes in cartilage. As the osteoblast differentiates during embryogenesis from a multipotent mesenchymal cell, a transcription factor (see below) called Cbfa1 upregulates the expression of osteoblast related genes. Among the early response genes are c-fos and c-jun; then genes appear coding in temporal sequence for histones, collagen type 1, alkaline phosphatase, osteopontin, and osteocalcin—a protein expressed at the peak of mineralisation—after which the matrix is remodelled. A sequence of genetic events occurs in proliferating chondrocytes, including expression of high concentrations of the secreted protein parathyroid hormone related peptide and then expression of a gene called Indian hedgehog (Ihh) as the chondrocytes become fully hypertrophic. This process is under further feedback control to prevent non-differentiated chondrocytes from moving down the hypertrophic pathway, thereby controlling the extent of longitudinal bone growth.

Cells in a state of senescence are no longer able to replicate, but they are not dead; indeed they are resistant to programmed cell death (apoptosis). Senescent cells show changed synthetic functions, such as increased collagenase production and reduced synthesis of tissue inhibitor of metalloproteinases—conditions that modify the tissues and organs and limit repair, as noted above, and contribute to ‘aging’ processes in situ in ways that are not really understood. Senescent cells have reached the end of their replicative life span because they are unable to progress from the G1 to S phase in the cell cycle. Mitogenic growth factors that induce quiescent cells to begin to traverse the cell cycle from G1 to S and beyond, still will not stimulate senescent cells to do so. The fundamental reasons for this block to progression in the cell cycle for senes-
cent cells are not fully known. When senescent cells are fused with replicating cells, cell division stops, and thus senescence is a dominant genetic trait. Information is emerging on modifications in a number of cell cycle regulators that may account in part for the senescent state: there seems to be loss of certain early response genes, overexpression of two inhibitors (p21 and p16) of critical growth promoting cyclin dependent kinases, and uninhibited activity of growth (tumour) suppressor genes. New insights have also become apparent relating to modifications in replicating cells that are part of the 'games that genes, viruses, and cells play': a mutant ras oncogene introduced into replicating cells considerably slows down their growth and induces, prematurely as it were, a senescence-like state.

Developments in molecular genetics have provided insights on modifications in collagen genes that result in skeletal growth abnormalities in humans. Two examples from many are type I collagen gene mutations (COL 1A1 and COL 1A2), associated with a syndrome of osteogenesis imperfecta; and type II collagen gene mutations (COL 2A1), which result in a range of spondyloepiphyseal dysplasias. A number of these latter syndromes have been described as 'type II collagenopathies'. One of the COL 2A1 mutations is manifested in affected families by normal stature but with premature primary generalised osteoarthritis. While opening up a new and important dimension in research, it has been suggested that most of the familial cases of osteoarthritis are not likely to be attributable to type II collagen mutations.

In animal models, an even wider range of genetic modifications—spontaneous or induced—are particularly instructive for observing the resulting phenotypic manifestations on the developing musculoskeletal system as the animal ages. Skeletal dysplasias have been the most intensively investigated with exciting new findings on genetic control of skeletal growth, but many of these studies are beyond the scope of this article. Table 2 focuses on selected examples of genetic modifications that result in phenotypic changes in the musculoskeletal system. The animal models of osteopetrosis, while an uncommon human clinical disorder, are important to illustrate how various genetic modifications at different developmental stages of osteoclast lineage and function result in impaired bone resorption and a similar phenotypic expression in the mouse— that is, dense bones. A spontaneous null mutation in the gene for macrophage colony stimulating factor-1 in op/op mice results in an inactive growth factor that normally is necessary for the maturation and function of certain cells of the mononuclear phagocytic system: osteoclasts and macrophages in bone, and the type A (macrophage-like) cell in the synovial membrane. The osteopetrotic (op) mouse model has been considered relevant to human osteoarthritis by virtue of the persistence of dense subchondral bone as the animal ages, during which time diaphyseal bone is restored to normal. Mice rendered deficient in either of two cellular protooncogenes, c-src or c-fos, show osteopetrosis resulting from impaired osteoclastic bone resorption, or failure of osteoclast lineage development, respectively. c-fos, which encodes a transcription factor, and c-src a membrane associated protein kinase, have the potential to become oncogenes when mutated. An insertional mutation in a mouse gene encoding a transcription factor termed mi TF results in microphthalmia, and induces formation of osteoclasts without ruffled borders and with poor bone resorbing capabilities, leading to osteopetrosis. Mice genetically engineered to overexpress a protein the authors called osteoprotegerin—a member of the TNF receptor superfam— exhibit a more benign form of osteopetrosis compared with those above, with a decrease in osteoclast numbers, apparently because of failure in maturation. Moreover, ovariectomised mice treated with osteoprotegerin maintained bone density. Mice deficient in PU.1, another transcription factor, lose a common haematopoietic progenitor for osteoclasts and macrophages, and this defect ‘may represent the earliest developmental osteopetrotic mutant yet described’—that is, earlier than mutations in CSF-1, c-fos, or c-src. On the other hand, overexpression of c-fos results in unrestrained osteochondral cell growth and sarcoma-like bone tumours. Mice with a deficient osteocalcin gene—a protein

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* Areas for potential clinical application (see text).
synthesised by osteoblasts in bone—show increased bone formation and improved bone quality. In this model, osteoclasts function normally, or even to a greater extent: ovariectomised osteocalcin deficient mice develop a more severe osteoporosis with oestrogen depletion than their normal ovariectomised littersmates.83 Matrix GLA protein (Mgp) is a mineral binding, extracellular matrix protein synthesised by vascular smooth muscle cells and by proliferating chondrocytes; in both instances their matrices are normally uncalcified. Mgp deficient mice, as they age, exhibit vascular and cartilage calcifications.84 Thus, these latter two ‘deficiency’ models show the normal capacity of osteocalcin to limit bone formation, and of Mgp to limit calcification processes in extracellular matrices of arterial blood vessels and cartilage. Future therapeutic interventions might be to develop antagonists to osteocalcin to promote bone formation, and agonists to Mgp to limit vascular and cartilage calcification. Mice with a targeted null mutation in the interleukin 6 gene maintain bone density after ovariectomy because of deficiency in osteclast function despite oestrogen lack.85 Certain osteoclast membrane molecules, called integrins, attach to matrix components, such as fibronectin or osteopontin, and initiate bone resorption. This process seems to be blocked by a synthetic integrin tested in vitro or injected into rats, which were then protected from bone loss after oophorectomy.86 Targeted disruption of the oestrogen receptor gene results in mice with osteopenia.87 These authors also describe a single clinical case, that of a 28 year old man with a mutated oestrogen receptor gene, who showed oestrogen insensitivity, pronounced with a mutated oestrogen receptor gene, who showed oestrogen insensitivity, pronounced osteopenia.88 Augmented expression of the gene for interleukin 4 in mice results in osteoporosis because osteoblastic bone formation is more severely decreased than osteoclastic bone resorption.89 One species of aging mice (C 57BL) spontaneously develops osteoarthritis; another (SJL/J), a form of muscular dystrophy.90 Deficiency in certain genes that control myogenesis results in various types of failure of muscle development.91 A number of transcription factors have been classified with respect to their structural/functional motifs in relation to the aging of bone92 and can be considered briefly in the light of genetic modifications shown in table 2. Many transcription factors become active in response to signals generated from the extracellular environment, and thus transduce these external signals to nuclear DNA to control the expression of specific genes that regulate differentiation processes.93 The c-fos protooncogene is a member of the so called leucine zipper family of transcription factors. The c-fos/leucine zipper motif is important for dimer formation with c-jun, a complex essential for forming the AP1 transcription factor complex, which in turn binds to the AP1 consensus sequence in the regulatory region of many genes, and stimulates their transcrip-

Conclusions

In the next several decades our society will experience an unprecedented challenge arising from the growth of the older population, particularly those surviving to very advanced age. Musculoskeletal disorders are widespread in elderly persons and have important public health implications. This article considers these challenges as opportunities, and presents some emerging health practices, particularly exercise programmes, that may extend a vigorous life style for older persons. Also discussed are newer diagnostic tests, and research studies that elucidate the development, maturation, and senescence of connective tissue cells in the aging process. Basic research is increasingly attentive to potential clinical applications, with prospects for early detection and therapeutic interventions that may ameliorate musculoskeletal disorders—especially osteoarthritis and osteoporosis—that exact such a high toll in suffering and expenditures. The combined endeavours of health providers and research scientists can become united in a common goal for the ‘whole health experience’ of older persons: not so much to extend the duration of life, but rather to improve its quality and preserve its vitality for a longer time.
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11 Yarasheski K E. The description of cellular senescence in this paper. Department of Cancer Biology, Life Sciences Division, Berkeley Laboratory, University of California.


