Osteoporosis Redux*

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This is an opportune time to review postmenopausal osteoporosis (PMO) given that our understanding of, and ability to diagnose and treat, the disease is evolving quickly. Osteoporosis and its consequences remain an important health problem in human and economic terms (*1*). Also, the prevailing conceptualization of osteopenia–osteoporosis is being challenged. The following issues in particular are in some flux and will be discussed in more detail:

- There is increasing recognition of the importance of bone structure as well as bone mineral density (BMD) as factors in fracturing.
- A range of measures is available in preventive care. These include fall prevention, dietary measures, and other lifestyle measures.
- A variety of anabolic and anticatabolic treatments for osteoporosis is now available.
- The assessment of patients is moving away from the prevailing World Health Organization (WHO) diagnostic classification to a more broadly based assessment of fracture risk.
- Many guidelines are now proposed for the management of osteoporosis, and these are broadly similar.
- The importance of fracture recognition is coming to the fore, matched by the introduction of dual-energy x-ray absorptiometry (DXA)–based vertebral fracture assessment.
- There is evidence of a considerable care gap in several aspects of diagnosis and treatment.
- The semiotics of osteoporosis as a disease are being questioned.

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DEFINITION

The definition of osteoporosis has evolved. Historically, the recognition of fractures constituted a diagnosis of osteoporosis. This has changed. The present understanding of osteoporosis provides a basis for prevention, diagnosis, and treatment aimed at avoiding or reducing fracture risk.

The definition currently proposed stems from a 2000 National Institutes of Health statement on the diagnosis and therapy of osteoporosis (*1*). It is as follows: "Osteoporosis: a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture."

This definition replaces an older definition (*2*): "Osteoporosis: a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture."

Those with a focus on diagnosis will note that there is a subtle downplaying of BMD in the more recent definition, in favor of a more generic statement about all the determinants of bone strength.

Both of these definitions are, nevertheless, more valuable in conceptual terms than of immediate relevance to patient care. In 1999, a WHO working group led by Professor John Kanis of Sheffield, England, developed and published a classification of osteoporosis in "postmenopausal white women." This classification was intended to be used for epidemiologic and planning purposes in determining and comparing the prevalence of the disease in various populations (*3*).

The classification depends on the use of DXA to measure BMD, and on a valid understanding of peak bone mass. Manufacturers of DXA machines have used either their own data or data from measurements of BMD in the proximal femur from the U.S. National Health and Nutrition Survey III (NHANES III) (*4*) to define mean peak BMD. The classification is then focused on the extent to which SDs of measured BMD deviate from a population-derived mean peak BMD, as achieved some time in adolescence or early adulthood. The NHANES III data suggest that BMD in the femoral neck then declines from the third to fifth decades of life at roughly 0.3% per year (*4*).

In the language of DXA, each SD from that mean peak BMD is described as 1 T-score, of either sign (*5,6*). By

contrast, the *z* score compares a patient's BMD with the mean of age- and sex-matched controls.

The proposed classification by T-score of patients was as follows:

- Normal: T-score of −1.0 or above.
- Osteopenia: T-score of −1.1 to −2.4.
- Osteoporosis: T-score of −2.5 or below.
- Established or severe osteoporosis: T-score of −2.5 or below and one or more prevalent low-trauma fractures (defined as fractures sustained in falls from a standing height or less, or an equivalent).

The rationale for the use of these numbers was that such a cut point for diagnosing osteoporosis yielded a prevalence of the disease similar to the incidence of osteoporotic fracturing in similar populations. Of course, there was no expectation that these populations, although similar in magnitude, would have comprised identical individuals.

No matter what was the intent of such a classification, it rapidly came to be used, first as a diagnostic paradigm and then as a series of intervention thresholds. Time has proved this to have been both good and bad. It has been good in bringing a focused approach to diagnosis, with diagnostic criteria that were readily understood and applied. The T-score is a simple unitless concept. The downside was an undue emphasis on DXA and BMD in fracture-risk estimation. Moreover, the diagnostic category of "osteopenia" has proved unsatisfactory in practice—to the point that some would prefer to see its use abandoned. The U.S. National Osteoporosis Foundation evidence tables supporting guidelines for diagnosis and treatment of osteoporosis make it clear that the relative risk of fracture in an osteopenic patient ranges from barely perceptible at T = −1.1 to virtually the same as that in an osteoporotic patient at T = −2.4 (*7*). Indeed, the International Society for Clinical Densitometry in a recent Position Development Conference debated rejection of the category of "osteopenia" but retained the definition, although expressing a preference for the description "low bone mass"(*8*). This may seem a semantic exercise, but there is a valid body of opinion that objects to putting a medical label on a group of people, many of whom simply belong in the lower end of the normal gaussian distribution of bone mass in any given adult population (*3,9*). This matter is further discussed below.

At a fundamental level, our understanding of the genetic and molecular pathways that result in the adult skeleton is increasing. These comprise the interactions of hormones, cytokines, and growth factors (*10*). Such insights promise new approaches to the treatment of osteoporosis (*10*).

EVIDENCE

In considering the evolving evidentiary basis for the diagnosis and treatment of osteoporosis, we have chosen to be explicit.

The evidence-based medicine movement (*11*) has been important both pedagogically and in introducing some rigor into reviews such as this. Critics of evidence-based medicine complain that it may obscure nuances of patient care, and we have all, unfortunately, become familiar with the heretical use of decision-based evidence-making—when evidence, or the lack of it, is used as a political tool in health policy development. Nevertheless, we have chosen not only to reference the statements we make in this review but also to categorize them as follows according to a hierarchy of the evidentiary support we found in making them:

- Level 1: conclusions based on prospective, double-blinded clinical trials.
- Level 2: conclusions based on systematic reviews and meta- or megaanalyses.
- Level 3: conclusions based on a Delphian process or arrived at by consensus or by a position development process, all involving "experts."
- Level 4: conclusions based on yet lesser degrees of evidentiary support.

Nevertheless, the evidentiary basis of medicine is a two-edged sword. Not only do guidelines, as we shall see, seek to constrain practice to interventions that are justifiable. They also reveal striking gaps that continue to deprive some people who might be osteoporotic from receiving optimal care (levels 2 and 3) (*12–14*).

THE LIFELONG GENESIS OF OSTEOPOROSIS

Long before recourse to diagnosis and treatment, the importance for an individual of achieving a maximum value of peak bone mass in early life is increasingly apparent. Indeed, it has been suggested, only partly in jest, that osteoporosis is a childhood disease. This is a way of emphasizing the apparent fact that concern about bone health should exercise society and individuals from early in life (level 1) (*15,16*). Throughout life, measures such as adequate weight-bearing exercise and sufficient dietary levels of calcium and vitamin D are fundamental to good bone health. Indeed, physical frailty and excessive or inappropriate medication use later in life contribute to a tendency to fall, with a consequent increase in the risk of sustaining a fracture. Such considerations emphasize a need to regard osteoporosis in the wider social context of health promotion.

A more radical view of this issue is provided by the Evolutionary Health Promotion initiative, which points to the stronger bones of our Paleolithic ancestors compared with our contemporaries at a given age—perhaps related to their greater serum concentrations of vitamin D from sunlight exposure, greater calcium intakes, diet in general, greater levels of exercise, and other comparable factors (level 3) (*17*).

THE RISK OF OSTEOPOROTIC FRACTURING

A number of risk factors for osteoporotic fracturing have been identified (level 2) (*7*). These include advanced age, low BMD, previous fragility fracture, family history of

osteoporosis or hip fracture, thinness (body weight < 58 kg) or low body mass index (<21 kg/m^2), glucocorticoid administration (for >3 mo), current smoking irrespective of amount, more than 2 alcoholic drinks per day, low calcium and vitamin D intake, and increased risk of falling (poor health, physical frailty, dementia, impaired vision, use of sedatives, limited physical activity).

Of these, increasing age and diminished BMD together with a history of low-trauma fracturing are the most powerful. The risks of falling are particularly amenable to management. However, despite many attempts to identify risk profiles, measurement of BMD for now represents, in the context of age, the best tool for the clinical evaluation of patients potentially having osteoporosis, although BMD accounts for only about 60% of bone strength (*5*).

BONE RENEWAL

Belying the impression afforded by the inert bone in a dried skeleton, bone is in a constant state of turnover and renewal in addition to its role in buffering serum calcium concentrations. The fact of bone turnover was observed as long ago as the 18th century (*18*). Because bone turnover occurs in a much greater degree in cancellous bone than in cortical bone, the impact of osteoporosis is most apparent in bone trabeculae. Bone remodeling is a local process characterized by, in succession, the formation of a resorption pit and its repair. The resorption phase lasts some 2–4 wk and the repair 10–20 wk (*18*). Under normal circumstances, these opposing trends are in equilibrium—that is to say, they are coupled until maturity, after which a small degree of mismatch occurs and its cumulative effect over a long time results in the loss of bone mass and a proclivity to fracturing that amounts to osteoporosis.

Bone resorption is effected by osteoclasts, which are large, multinucleated cells derived from hemopoietic cell lines. Repair is effected by osteoblasts derived from mesenchymal progenitors. The resorption pit results from local changes in pH and hydrolytic enzyme activity that cause the minerals and proteins to become soluble (*18*).

A third cell line is found in bone—osteocytes—and is derived from matrix-producing cells. They become embedded in the bone matrix, and their precise role remains uncertain, but they are believed to transduce signals arising from mechanical strain in bone.

Bone turnover can be increased systemically—for example, by mechanical influences (immobility and weightlessness) and hormonal effects (glucocorticoids, thyroid hormone excess, estrogen deficiency) and locally by an inflammatory process (rheumatoid arthritis, periodontal disease). The complex feedback systems that maintain bone homeostasis are as yet incompletely understood. They appear to involve a complex set of cellular and chemical mediators.

The formation and breakdown of protein in a resorption pit results in increased concentrations of specific enzymes and protein fragments in blood or urine. Examples are bone-specific alkaline phosphatase and pyridinoline-containing cross-linking peptides such as C- and N-telopeptides (*19*). These are increasingly used in the management of PMO and other metabolic bone diseases—for example, in testing patient compliance with drug regimens. However, they will complement but not replace studies of bone mass. Their use is best understood by analogy with a bank account: Bone markers reflect the equivalent of the number and timing of transactions in the fund where BMD measures the size of the principal in the deposit.

DIAGNOSIS

Investigators have identified several techniques by which to examine bone and, in particular, to measure BMD. A comparative analysis of the most widely used of these techniques has shown that, in patients at risk, all of the credible methods have some capacity to identify the relative risk of fracturing (level 2) (*20,21*). There is also an element of site specificity in that measurements at any particular site tend to best predict fractures at that site (level 2) (*21,22*). Nevertheless, in general, any validated measurement of bone does have potential applicability to the clinical problem of osteoporosis (levels 2 and 3) (*20*).

North American practice is heavily focused on the use of DXA. This focus relates more to the availability of an effective population database to provide the normative grounds for diagnosis using the WHO classification (*3*) than to any a priori technical supremacy enjoyed by DXA (*21–23*). Nevertheless, it is important to realize that the database for DXA, whether it be the one developed by specific manufacturers or that derived from the NHANES III study (*4*), is unique to DXA, at least for the present. Thus, although, for example, quantitative ultrasound (QUS) and quantitative CT (QCT) are calibrated to provide T-scores by their respective manufacturers, such scores do not equate with the T-scores used in the WHO diagnostic classification of osteoporosis, described above (*3*), in any simple way. They relate to different, and usually smaller, manufacturer-specific databases.

Competing social priorities have led to differences in technologic practice in various countries such that QUS, for example, is much more widely used elsewhere in measuring bone than is the case in North American practice. DXA machines in North America vastly outnumber those elsewhere in absolute terms, let alone on the basis of respective populations.

The diagnostic technologies available are conveniently divisible into those that, on the one hand, examine the central skeleton—spine, proximal femora—and those that, on the other hand, examine the peripheral skeleton (often designated by the prefix "p"). Some machines do both: For example, DXA machines will usually serve for pDXA of the forearm.

THE CENTRAL SKELETON

Dual-Photon Absorptiometry

Examinations of the central skeleton began with a radionuclide source (^{153}Ga) emitting γ-rays of 2 discrete energies.

The technique sampled bone and adjacent soft-tissue attenuation, usually in the lumbar spine, proximal femur, and forearm, with whole-body measurements an option. The differential attenuation of the 2 energies allowed correction for soft-tissue attenuation. The result was similar to DXA in giving a measure of "areal," rather than volumetric, density. Dual-photon absorptiometry contributed important data to our understanding of osteoporosis but has been almost entirely superseded by DXA (*22*).

DXA

As stated above, DXA is a dominant technology used in osteoporosis diagnosis in North America, and in much research published in the last 2 decades, not least for being the basis of the WHO classification cited (*3,22–24*). The only fundamental difference from dual-photon absorptiometry is that the radionuclide source is replaced by an x-ray tube (*25*). The fact that the photon flux is both much higher and not subject to a decrease as the source decays improves the logistics of densitometry and removes the statistical uncertainties related to making measurements of changing sample sizes. DXA is a pragmatic approach to BMD measurement for clinical purposes but it suffers from limitations, which include the following (*26*):

- Measurements are of "areal density," an artificial construct.
- Results are influenced by body weight, fat distribution, and weight change.
- Results are influenced by bone size independently of BMD because the use of areal density ($g \cdot cm^{-2}$) does not account for variations in the orthogonal dimension.
- The regions of interest, in the proximal femur in particular, are not consistent between manufacturers.
- Data are manufacturer-specific.
- Measurements are influenced by artifacts, chiefly degenerative disease, especially in the spine.

These and other advantages and disadvantages of DXA have recently been critically reviewed (*26*).

Common pitfalls in DXA interpretation are to describe low BMD as "bone loss" in the absence of serial studies; to use descriptors such as the patient "having the bones of a 75-y-old" when age is in reality an independent predictor of fracture risk; to use the Ward's triangle region of interest (because it samples a small volume, was not part of the WHO classification, and leads to overdiagnosis); and a failure to use the DXA "images" as a quality improvement tool in respect to artifacts and patient positioning. Any laboratory contemplating serial measurements ideally needs to establish its own precision performance (level 3) (*27*).

Measurements of hip-axis length, femoral neck-shaft angle, and femoral neck width in conjunction with DXA examinations are possible. So there remains the uncertain but promising potential for DXA to be used to provide structural data as well as BMD measurements (*28*).

QCT

CT is inherently quantitative, but the Hounsfield numbers used in conventional radiologic practice are dimensionless and relative. Inclusion of a set of hydroxyapatite standards in the field of view permits creation of a calibration curve to obtain a truly volumetric BMD in $g \cdot cm^{-3}$. It is necessary to ensure proper positioning of the region of interest to avoid partial-volume artifacts. At present, the technique can be used in the lumbar spine and proximal femur, and at least one manufacturer has developed an internal calibration method. Retrofits of various kinds are available for all CT scanners, and spiral CT is equally capable of providing data that highly correlate with BMD measurements (*29*). In vertebral bodies, BMD measurements of purely cancellous bone are possible (*30,31*). Also, there is the prospect of combining BMD measurements with analyses of cancellous bone architecture either in the spine or in the peripheral skeleton using either QCT or pQCT (*30–34*).

THE PERIPHERAL SKELETON

A number of commercial machines for bone measurements of the peripheral skeleton are available. The sites involved include the distal forearm, calcaneus, phalanges, and tibia. Grampp's data indicate that these methods are all potentially valid in the context of risk assessment (*20*). However, for serial measurements the methods are less useful. On the one hand, BMD in the peripheral skeleton is slow to change, either with disease or with treatment. Add to this the lower precision of most peripheral technologies (*35*) and it is clear that measurements of the least significant change using them will have limited use in clinical care (*35*).

Peripheral Single-Energy Photon Absorptiometry

Like dual-photon absorptiometry, single-energy photon absorptiometry used a radionuclide source to measure BMD in the distal forearm. Again like dual-photon absorptiometry, single-energy photon absorptiometry provided many insights into fracture risk and the epidemiology of osteoporosis but has been effectively replaced now by other methods of peripheral densitometry or measurements directed to the central skeleton (*36,37*).

Peripheral Single-Energy X-Ray Absorptiometry

Single-energy x-ray absorptiometry machines are available for measurement of radial, calcaneal, and phalangeal bone densities (*37*). The differences between the machines, especially with respect to the regions of interest used, make direct comparisons difficult.

pDXA

Central DXA machines may be used to examine the forearm, or there is a dedicated pDXA machine available calibrated to measure BMD in the calcaneus (*37*).

QUS or pQUS

One of the difficulties in making a simple generalization about QUS is the sheer technologic diversity involved. Thus, as of November 2005, there were 20 machines available to measure bone, 8 of them approved for use in the United States. Each is in some way unique, making comparisons difficult (*38*).

Ultrasound attenuation and the speed of transmission of sound are the variables quantitated (*38,39*). Both are influenced by BMD, but other variables such trabecular orientation and even ankle edema can modify results (*36,37*). By definition, QUS differs from conventional ultrasonography in usually requiring 2 transducers. Measurements of speed-of-sound transmission alone or with broadband ultrasonic attenuation are variously made. These are sometimes combined by manufacturers to provide a composite figure such as "BMD equivalent" or "stiffness," but it is important to recognize that stiffness has a quite different definition in materials science. Such combined indices use weighted values to improve discrimination between fracture-prone and normal populations. A further difference between machines is to be found in the means used for acoustic coupling of the transducer with skin—with ultrasound gel, a water bath, or water bags all being used in different configurations.

The bone measured is most often the calcaneus, but the patella, phalanges, and long bones are among other choices that have been made.

An early hope with respect to QUS was that it might reveal some aspect of bone other than BMD. Parallel DXA and QUS measurements of the calcaneus have vitiated that expectation. It seems that BMD is the primary factor in the changes in broadband ultrasonic attenuation and in speed of sound with age (*36*). Nevertheless, although QUS has recently been found wanting in a metaanalysis (level 2) (*39*), it does have the potential to cheaply discriminate between high and low BMD, and perhaps its use in such a way may provide a tool for use in underserviced and remote areas or as a means of identifying patients requiring further investigation.

pQCT and pMRI

These techniques use a small-aperture CT or MRI scanner to do either volumetric density measurements and imaging (CT), or imaging alone using MRI, of bones such as the distal radius. The real potential may be in obtaining high-resolution images of cancellous bone architecture in search of a measure of bone quality (*33,40*).

The many techniques and technologies available to assess bone create a potential minefield in choosing between them, particularly when it comes to comparing data from different studies. Because all of these methods have some utility, a clinician needs to know the answers to the following:

- When the technology involves several regions of interest, which are validated and of clinical relevance?
- What is the nature of the database used?
- Has the database been validated?
- What is the measured accuracy and, in particular, the precision of the test?
- How do the measurements relate to the WHO diagnostic classification of osteoporosis?
- How are the data that are obtained from a test best synthesized into a comprehensive risk estimate?
- What is the technologic support available?

SKELETAL RADIOGRAPHY

Fracture risk is compounded of BMD, bone quality, and the other risk factors, of which the most easily quantitated is age but also proneness to falls and physical frailty.

By bone quality is meant all of the other variables in bone in addition to BMD that contribute to bone strength or weakness. It is not yet, however, a precise concept but is made up of factors such as bone architecture (or geometry), trabecular connectivity and connectivity-density, cancellous porosity, bone plasticity, microdamage, and fatigue injury and its repair (*40*). The importance of each factor may well be different in each individual, and an important understanding is that BMD and bone quality are to some extent independent variables. Unfortunately, although DXA permits a diagnosis of osteoporosis on the basis of BMD before fracturing occurs, techniques to examine bone quality have not yet made the transition from the research laboratory into the clinic. Radiographs giving evidence of low-trauma fractures may nevertheless provide evidence of abnormal bone quality when skeletal mineralization is only modestly abnormal and thus may play a key role in patients who fracture when BMD values are only slightly reduced.

Thus plain-film radiography remains important in recognizing bone fragility. Of osteoporotic fractures of the spine, about 60% occur without causing any symptoms at least in the short term. The recognition of such fractures will thus most often depend on chance. Spinal radiographs may be obtained for other indications, or the thoracic spine may be seen incidentally to lateral chest radiography. An opportunity thus exists to recognize and treat undiagnosed osteoporosis from radiographs and radionuclide bone scans. Numerous studies have shown that such fractures predict further fracturing, to say nothing of morbidity and mortality, with power as great as or greater than a densitometric diagnosis of osteopenia (level 1) (*41–43*). Unfortunately, a weight of evidence indicates that this opportunity is being missed with respect to identifying vertebral fractures incidental to radiologic examinations, for example of the chest (level 3) (*44–46*).

As a result, there has been a series of international educational initiatives attempting to address this problem (*47–51*).

DXA-BASED VERTEBRAL FRACTURE ASSESSMENT

The introduction of densitometry machines capable of being used for vertebral morphologic assessment by lateral

spinal radiography (Fig. 1) is a response to the increasing recognition given to spinal fractures as predictors of further morbidity and mortality as noted above (*52,53*). The International Society of Clinical Densitometry has suggested that these spinal images obtained by DXA devices (usually lateral), variously described by the respective manufacturers, are best described generically as vertebral fracture assessments. The spinal images produced are not of radiographic quality but often permit the recognition of fracturing. In practice, grade 1 fractures, as defined by the classification of Genant et al. (*54*), prove difficult to identify, whereas the images, particularly of the upper thoracic spine, may prove not to be of diagnostic quality (*53*).

Using edge-detection software, it is even possible to identify and measure vertebral deformations, but that technical capability at present exceeds a firm understanding of what constitutes minimal vertebral fracturing and its description in quantitative terms.

No study even approaching a cradle-to-grave design has been performed to allow for a foolproof definition of vertebral fractures. Nevertheless, there are both longitudinal and cross-sectional studies of vertebral fracturing. Also, the pivotal trials of the bisphosphonates and most subsequent treatments all used incidental vertebral fractures as an outcome measure. Thus, there is a basis for diagnosing vertebral fractures, although debate about the subtleties of such a diagnosis continues (*55,56*). Although several sets of criteria for diagnosing fractures have been published, a widely accepted method, used in the trials noted, is the method of Genant et al. (*54*), although among the limitations of the Genant tool is that the fracture categories overlap.

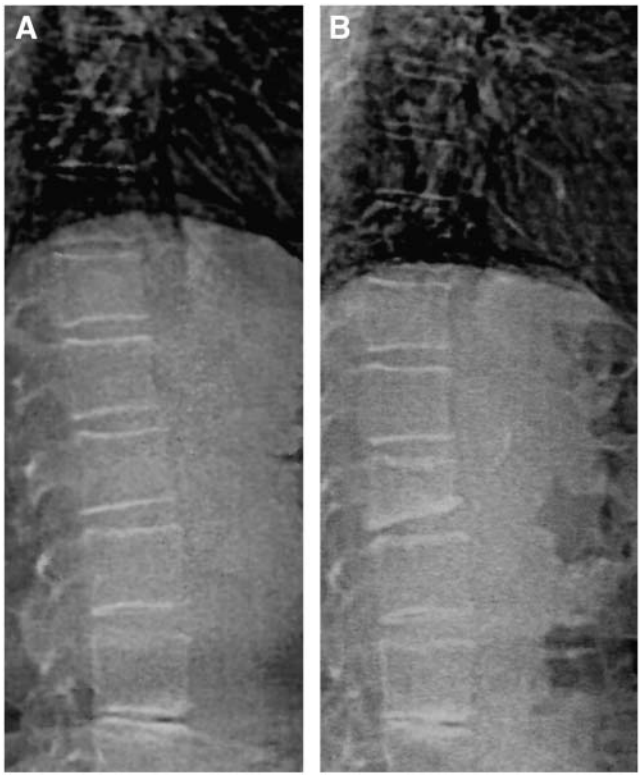

FIGURE 1. Images from March 2002 (A) and June 2006 (B), with the latter revealing an incidental superior end-plate fracture of L3 diagnosed on this DXA-based vertebral fracture analysis. Although the images are not intended for other diagnostic purposes, intervertebral disk disease is evident on both images.

THE CARE GAP IN OSTEOPOROSIS

It has become apparent that there are serious care gaps in the recognition and treatment of established osteoporosis. These gaps occur in so many dimensions that there is plenty of blame to spread around the many specialty groups involved.

Vertebral Fracture Recognition

Gehlbach et al. (*44*) examined chest radiographs obtained in the emergency room for 934 women aged 60 y or more. Of this group, 132 had one or more spinal fractures as defined by the semiquantitative criteria described by Genant et al. (*54*). However, of the 132 fractures, only 65 (49%) were reported by the radiologist examining the chest radiograph. Of the fractures reported, only 17 (13%) were noted as a discharge diagnosis in the medical record, and, worse yet, only 25 (19%) of the patients with fractures were treated (level 4). Such findings have been confirmed by Canadian and European data (levels 1 and 4) (*45,46*).

Systemic Treatment of Osteoporotic Fractures

There are equally compelling data to indicate that patients with low-trauma fractures treated by casting or hip replacement are rarely investigated for underlying osteoporosis, much less treated if they should have the disease (level 4) (*57–62*).

Anecdotal accounts also describe patients referred for vertebroplasty without their receiving systemic therapy for underlying osteoporosis. A recent publication summarizes the comprehensive approach necessary for the care of individuals with osteoporotic fracturing (level 2) (*63*).

RISK ASSESSMENT

Instead of or in addition to using the DXA-based WHO disease classification (*3*), there is an international move to incorporate BMD results into a more broadly based fracture risk assessment. The WHO has served notice in a press release that it has a task force working in this context, notably again led by Kanis (*64*). One system of risk assessment had already been published by Black using data from the "Study of Fractures," and the risk factors considered included age, fracture history after age 50 y, family history of fracture, smoking history, being underweight, and a measure of physical frailty—the ability of patients to rise from a sitting position without use of their arms (level 3) (*65*). Osteoporosis Canada has also convened an "expert panel" that has published a system of absolute fracture-risk

assessment based on BMD, age, fracture history, family history, and glucocorticoid administration (level 3) (*66*).

Notably, these approaches have in common that they provide fracture risk as a 5- or 10-y percentage. Relative risk, especially, has a great potential to be misleading in this context. (Large relative risks applied to tiny risks still result in small absolute risks.)

The WHO approach will, we are promised, encompass global data and use either BMD or body mass index, as well as other risk factors such as those noted above. However, each region or country will then be invited to deduce the risks to its citizens based on specific fracture incidence or prevalence data in that jurisdiction. Moreover, the intention is that intervention thresholds for treatments will then be arrived at in each country or population on the basis of cost-utility analyses and the willingness to pay in each of the societies concerned.

TREATMENT

The management of osteoporosis is complex, and the following summary is meant to provide an overview for the diagnostician. Clinicians involved will require more information.

Lifestyle Modification

The patient having bone loss may potentially benefit from several strategies. Falls are the cause of nearly 90% of fractures (*67*), and in North America one third of women aged over 60 y fall at least once a year (*68*). Thus, fall prevention (*69*), as well as measures to minimize the effect of falls by the use of hip pads, is recommended although a systematic review has found that hip pads are of uncertain efficacy (*70*). In addition, lifestyle modifications (including exercise and adequate calcium and vitamin D intakes) also form the backbone of patient management independently of decisions about the use of drugs.

Calcium and Vitamin D

It is apparent that northern latitudes (*71*), as well as clothing choices (*72*), may limit the production of bioactive vitamin D in human skin (level 3). Particularly in the elderly, there may also be subclinical deficiencies of dietary calcium and vitamin D (*73*). Chapuy et al. demonstrated a reduced incidence of hip and other nonvertebral fractures in very elderly, institutionalized women treated with daily calcium and vitamin D (level 1) (*74*). Indeed, it has been suggested that the vitamin D requirements for optimal health greatly exceed current dietary recommendations (level 3) (*75*).

Therefore, it is usual now to recommend high levels of calcium and vitamin D with increasing age—in the diet or, if necessary, as supplements—and specifically 1,500 mg of calcium daily and 800 units of vitamin D at age 80 y and over. Calcium and vitamin D administration formed part of the medication for the treated and control groups in the pivotal trials of osteoporosis medications, and these nutrients should accompany any other medication.

Other lifestyle recommendations include smoking cessation and limitation of alcohol intake (no more than 7 drinks a week) (*76*).

Pharmacologic Management

Although lifestyle modification may suffice for patients with a low risk of osteoporotic fracture, potent medications now exist to treat those at greater risk.

For some time, the treatment of osteoporosis has been dominated by the group of drugs formerly described as antiresorptive agents and amounting to the first- and second-generation bisphosphonates. It has recently been suggested that these might be better described as anticatabolic agents to contrast them with the newer anabolic therapies that have now become available. The fracture efficacy of the drugs available is summarized in Table 1.

TABLE 1
Reported Fracture Efficacy of Drugs Used or Proposed for Use in Treating Osteoporosis in Postmenopausal Women Irrespective of Diagnostic Method

Class of drug	Agent	Fracture efficacy			Evidence
		Proximal femur	Spine	Other	
Nutritional	Calcium	+			Level 1
	Vitamin D (at 700 or 800 IU/d)	+		+	Level 2 (*131*)
Antiresorptive	Alendronate	+	+	+	Level 1 (*75–76*)
Anticatabolic	Risedronate	+	+		Level 1 (*75,77*)
	Ibandronate		+		Level 1 (*78*)
	Calcitonin		+ (at 1 dose only)		Level 1 (*79*)
	Raloxifene (SERM)		+		Level 1 (*83*)
Mixed	Strontium ranelate	+	+	+	Level 1 (*87,88*)
Anabolic	Teriparatide	+		+	Level 1 (*81*)

SERM = selective estrogen-receptor modulator.
It should be recognized that not all trials are powered to reveal the full spectrum of fracture efficacy and that these data have also been subject to critical review questioning some interpretations (*92*). Also, not all these data apply to all patients.

The Bisphosphonates

The bisphosphonates are kissing cousins of the agents used in bone scintigraphy, and it is a cultural divide between specialties that leads to the distinct use of *bis*-phosphonates and *di*-phosphonates as terminology, perhaps depending on the bias of one's classical education.

Bisphosphonates act to limit bone resorption and thus increase bone mass. However, that their action is more complex than this simple fact suggests is indicated by their proportionally greater action in reducing fractures than in affecting BMD. The second-generation drugs (alendronate, ibandronate, risedronate, and their successors [Table 1]) differ from the first generation (etidronate) in being organic—having an amino group—but the differences are more profound than this simple fact might suggest. Etidronate is approved in the United States only for the treatment of Paget's disease of bone.

The pivotal trials of the bisphosphonates have clearly demonstrated a significant ability to increase BMD and, more important, a significant fracture prevention outcome (level 1) (*77–80*) occurring within the first year of administration. The optimal duration of therapy has, however, yet to be established.

Of interest in the context of the complex nature of bone strength, the proportional reductions in fracture risk are much greater than the proportional increases in BMD after treatment such as bisphosphonate administration.

Calcitonin

Salmon calcitonin, administered either subcutaneously (except in Canada) or as a nasal spray, is available to treat osteoporosis (in the United States it is not approved for prevention). This agent also inhibits bone resorption, although less well than the bisphosphonates. It is particularly effective in controlling the pain from vertebral fractures (*81*). The nasal spray reduced recurrent fracture risk in a 5-y prospective study at one dose, but there has been skepticism about these data in that there was a paradoxic absence of a dose–response relationship at other doses. Changes in BMD were observed only in the spine and then only at the highest dose used (level 1) (*82*).

Parathyroid Hormone

Various fragments of parathormone are in use or being considered as potential agents for treating osteoporosis. These are made either by synthesis or from recombinant products. The 34-amino-acid N-terminal fraction of parathormone (teriparatide) is an anabolic agent that stimulates osteoblastic bone formation, increasing BMD, trabecular connectivity, and bone size (*82*). Daily subcutaneous injections have been shown to reduce fracture risk in women with existing vertebral fractures (level 1) (*83*). It is a very powerful and effective drug, but present constraints suggest that it should not be administered indefinitely but used over 1–2 y and then replaced with an anticatabolic agent. Potential intervals between treatments have yet to be established.

The indications for teriparatide are broad, but it may have particular merit in patients with osteoporosis who are at high risk of further fracturing in the short term on account of a fracture history, who have multiple risk factors, or who have failed to respond to or have been intolerant of other therapies. Against its powerful attributes must be set the fact that it is expensive and requires parenteral administration. Presently under investigation in the context of osteoporosis is the parathormone molecule itself (made up of 84 amino acids) and a 31–amino acid N-terminal fragment.

Estrogen and Selective Estrogen-Receptor Modulators

Although estrogen is approved in North America for osteoporosis prevention, but not treatment, the Women's Health Initiative findings of the side effects of estrogen therapy have changed the focus of hormonal therapy (*84*). Estrogen increases BMD in proportion to dose (level 1), and the Women's Health Initiative found a global reduction in fracture risk associated with estrogen and progestin (level 1) (*84*). Selective estrogen-receptor modulators act as estrogen-receptor agonists or antagonists or both. Raloxifene is one such drug available at present, and others are under investigation. It increases BMD and results in a 55% reduction in vertebral fracture risk in osteoporotic women. However, the risk of other fractures was not statistically significantly different (level 1) (*85*). At the same time, the risk of breast cancer was reduced (*86*), and in the final analysis there was no increase in cardiac or cerebral events (level 2) (*87*) although the trial was not designed to test these outcomes.

Strontium Ranelate

There has long been an interest in the potential of strontium salts to alter bone strength. Strontium ranelate has emerged as one compound the use of which is supported by good evidence. It appears to combine both modest antiresorptive (anticatabolic) and anabolic actions, and although its mechanism of action is yet to be fully worked out, bone formation and resorption appear to dissociate (*88*).

Densitometrists need to be aware that the Z of strontium results in changes in the electron density of bone and, therefore, in the apparent BMD in patients on this drug, some of which are due to incorporation of the strontium into bone mineral. Treatment effects on BMD are thus amplified by as much as 50%, and a correction factor should be applied (*89*). Given this constraint, increases in BMD and decreases in vertebral fracture risk were observed, with the trial not being powered to measure nonvertebral fracture risk (level 1) (*89,90*).

Potential Therapeutic Agents

There are theoretic grounds to suspect that thiazides and the statins may positively influence bone mass. However, no drug of either group has been actively investigated in this context. At the bench there is interest in the potential to block the osteoprotegerin/RANKL/RANK osteoclast receptor system, and a vaccine or monoclonal antibody against

RANKL is of potential interest. Denosumab is a human IgG_2 antibody against RANKL (blocking the binding of RANKL to RANK) that has been subject to preliminary clinical investigation (*91*), and undoubtedly, an increased understanding of the molecular basis of bone turnover will yield further insights and therapeutic opportunities.

Side Effects

The safety profiles of the drugs used in osteoporosis are generally not threatening. The inconvenience of taking bisphosphonates early in the morning on an empty stomach has been relieved in part by dosage schedules that allow dosing at weekly or longer intervals. Some patients still have esophageal and gastric irritation, however. The use of parenteral ibandronate carries a theoretic risk of causing renal failure, and a theoretic concern also exists about oversuppression of bone turnover with long-term bisphosphonate therapy. There have been recent reports of osteonecrosis of the jaws occurring in patients on the bisphosphonates, particularly if they are on both very high doses and concurrent cancer medication (level 2) (*92*). Osteonecrosis of the jaws is a poorly characterized and understood disease, but this risk is probably small, particularly in patients being treated for osteoporosis at the recommended doses. Meanwhile, there is no clear evidence dictating the optimal duration of bisphosphonate therapy, although it is known that bone turnover remains relatively suppressed (level 1) (*93*).

The side effects of estrogen and selective estrogen-receptor modulators have been alluded to. Teriparatide has been associated with a small incidence of hypercalcemia, dizziness, and muscle cramps. High doses in a rat model have caused osteosarcomas, but the species is prone to this disease and had open epiphyses. Nevertheless, as noted, it is recommended that treatment should not be extended beyond 24 mo and needs to be followed by antiresorptive therapy. Drug-related adverse events associated with strontium ranelate therapy were, in the reported trials, uncommon but included nausea and diarrhea (*84*).

Fracture Efficacy

Table 1 summarizes the data concerning the efficacy of medication in reducing fracture risk. Although these findings come from successive pivotal trials and have been reviewed with respect to the bisphosphonates (*94*), Meunier also published a critical review (before the findings with respect to strontium ranelate were published) (*95*). He found, using 5 explicit criteria, that only 3 medications were effective in reducing fracture risk: alendronate (with respect to spinal, proximal femoral, and wrist fractures diagnosed clinically and spinal fractures diagnosed radiographically), raloxifene (with respect to radiographic spinal fractures), and vitamin D and calcium (with respect to clinically diagnosed hip fractures). It should be noted that not all trials have been powered to allow for determination of relative risks for all fractures.

GUIDELINES

There is a minor industry concerned with the promulgation of guidelines for both the diagnosis and the management of osteoporosis. A large number are currently listed on the Web site of the International Osteoporosis Foundation (*96*). Bonnick has provided a summary of guidelines, but it is important to realize that this is understandably North America–centric in its focus (*97*). An interesting dialogue concerning differences of opinion in this context has resulted between Kanis and his colleagues, speaking for the International Osteoporosis Foundation (*98*), and officers of the International Society of Clinical Densitometry (*99*), defending the perspective of the International Society of Clinical Densitometry Position Development Conference of 2003 (*8*). At the risk of oversimplification, the differences arise from 3 sets of factors:

- Differences in interpretation of the evidence, itself not always complete or sufficient, on the use of population-screening techniques in osteoporosis.
- The different weights given to competing social priorities in health care policy development, and the contrast between gross domestic product and the proportion of gross domestic product spent on health care. Figures for the United States (per capita gross domestic product, $37,600; 13.9% spent on health care) and Great Britain ($25,300 and 7.6%, respectively) are quoted as examples of local constraints (*98*).
- Regional differences in fracture risk (*100,101*).

A range of guidelines concerning the use of DXA in population case-finding have been promulgated, some of which follow (levels 2 and 3):

- American Association of Clinical Endocrinologists (2001) (*102*).
- American College of Obstetricians and Gynecologists (2002) (*103*).
- Canadian Task Force on Preventive Health Care (*104*).
- International Osteoporosis Foundation (European Consensus) (*105,106*).
- National Osteoporosis Foundation (United States) (1998) (*7*).
- North American Menopause Society (2002, 2006) (*107*).
- Osteoporosis Canada (1996, 2002) (*108,109*).
- Royal College of Physicians of Great Britain (1999) (*110*).
- U.S. Preventive Services Task Force (2002) (*111*).
- WHO (1994) (*112*).

These guidelines are to various degrees evidence-based, with the National Osteoporosis Foundation, Osteoporosis Canada (2002), and WHO guidelines being among the most explicit in this context (level 3). However, looked at from an independent perspective, most guidelines in this context are found to lack rigor (*113*). A broad consensus can be

identified between the documents developed in North America concerning the use of DXA, as follows:

Bone mineral density should be measured in the following groups:

- All menopausal women aged 65 y or older.
- All menopausal women younger than 65 y but with one or more risk factors.
- Premenopausal women (aged 40 y or more) with one or more low-trauma fractures.
- Women being treated for osteoporosis.
- People of either sex beginning or receiving long-term glucocorticoid therapy.

Treatment guidelines, where articulated, are less consistent but tend to focus interventions, other than calcium and vitamin D, on those with low-trauma fractures, T-scores of −2.0 or −2.5 or less, or both.

It must be noted that, in many jurisdictions, no support for population-based use of DXA or the clinical strategies described above has been deduced.

This debate is not confined to Europe and North America. Broadly based guidelines (with multispecialty input) have been published, for example, from Lebanon (and endorsed by the Eastern Mediterranean branch of the WHO) (*114*) and by the Royal Australian and New Zealand College of Radiologists (*115*).

SECONDARY OSTEOPOROSIS

Our intention here has been to review PMO. However, a variety of diseases associated with either poorly mineralized bone or bone loss may mimic osteoporosis (Table 2) (*116*). It has been suggested that it may be realistic to consider them as risk factors having an impact additional to that of inadequate peak bone mass, hypogonadism, and age-related changes (*116*). Some of the diseases are indistinguishable from PMO and may, with some justification, be otherwise described as causes of secondary osteoporosis. Others are causes of low bone mass that are indistinguishable from PMO on densitometry but have a distinct pathophysiology. It is a matter of usage to decide if myelomatosis, as one example, should be described as an example of secondary osteoporosis, but it certainly enters into the differential diagnosis of low-trauma fracturing and abnormally low BMD. Moreover, the complexity of this matter is illustrated by the evidence suggesting that an osteoclast-stimulating factor is secreted in myeloma (*117*).

Of the causes of acquired secondary osteoporosis (*116*), gonadal insufficiency may lead to osteoporosis related to causes other than menopause. Glucocorticoid excess (due to disease or, more usually, oral medication) is notable for the rapid rate and large degree of bone loss that results, with the changes being more conspicuous in cancellous than in cortical bone. Glucocorticoids may interfere with calcium absorption in addition to having a direct effect on bone. There are conflicting data about the impact of inhaled high doses of the drug. Patients being prescribed glucocorticoids should have their BMD measured at the outset and may need 6-monthly follow-up. Thyroid hormones (both thyroxine and triiodothyronine) accelerate bone turnover by shortening the remodeling cycle in a dose-dependant way (*118*) and, in the long term, influence BMD (*119*). It has proved difficult, however, to distinguish the effects of thyroid hormone treatment and preexisting thyrotoxicosis in patients with thyroid disease, but 1 report of a careful study indicates that the lowest effective suppressive doses of levothyroxine were not associated with bone loss in premenopausal women (level 1) (*120*). Thyrotoxic bone disease appears, moreover, to be reversible when the thyrotoxicosis is treated.

Renal failure may cause increased bone resorption, decreased bone formation, or both.

Another current issue in this context is the potential need for treatment of patients using intramuscular medroxyprogesterone acetate as a contraceptive. This agent has been found to cause bone loss, but it appears to be reversible (although again there are conflicting data) and the current

TABLE 2
Some Secondary Causes of Bone Loss

Category	Cause
Medications	Oral or parenteral glucocorticoids for more than 3 mo
	Excessive doses of thyroxine
	Aromatase inhibitors
	Phenytoin
	Heparin
	Cytotoxic and immunosuppressive agents
	Intramuscular methoxyprogesterone
Genetic disorders	Osteogenesis imperfecta
	Thalassemia
	Hypophosphatasia
	Hemochromatosis
	Disordered calcium balance
	Hypercalciuria
	Vitamin D deficiency
	Endocrine disease
	Cushing syndrome and disease
	Gonadal insufficiency
	Hyperthyroidism
	Type 1 diabetes mellitus
	Primary hyperparathyroidism
	Gastrointestinal disease
	Malabsorption syndromes
	Chronic liver disease
	Prior gastrectomy or gastroenterostomy
Other disorders	Myeloma, lymphoma, and leukemia
	Systemic mastocytosis
	Nutritional disorders (e.g., anorexia nervosa)
	Rheumatoid disease
	Chronic renal disease

Adapted from (*107*).

WHO recommendation is that persons using medroxyprogesterone acetate do not need BMD measurements (*121*), still less any bone-active medication. The same is largely true of the use of gonadotropin-releasing hormone, which causes iatrogenic hypogonadism, but in this case the bone loss may be offset by concurrent low-dose estrogen therapy.

There is good evidence that so-called secondary osteoporosis is not uncommon. In evaluating patients, it is wise to use a few selected investigations to exclude this possibility (such as blood cell count and the concentrations of serum calcium, 25-hydroxyvitamin D, alkaline phosphatase, serum protein, urinary calcium, urinary cortisol, and, depending on clinical findings, serum TSH) and be alert to the fact that a disproportionately low (age- and sex-matched) Z may also point to secondary disease. Issues of calcium and vitamin D deficiency should be addressed using the current dietary recommendations relating to these nutrients.

OSTEOPOROSIS AS INFLUENCED BY ETHNICITY AND RACE

Because of regional differences in fracture prevalence and BMD (*122,123*), it has become the conventional wisdom that race (usually equated with cultural differences between peoples) and ethnicity (usually equated with genetic differences between peoples) influence BMD and fracture rates. Some of these differences are real. BMD values at all ages and in both sexes are higher in black than white North Americans (*123–126*). However, genomic differences between peoples from different continents are trivial compared with the similarities. In addition, the U.S. population is outbred to an increasing extent. Thus assumptions about race and ethnicity are increasingly being deconstructed and these are seen as surrogates for other sociocultural variables (*127,128*). It is increasingly the case that ethnocultural differences in disease prevalence and severity are seen to be markers of other socioeconomic factors at work, and this fact, combined with the increasing genetic diversity of populations, suggests that in the future the field will best focus on dietary and other factors in osteoporosis rather than on the uncertain influences of race and ethnicity.

OSTEOPOROSIS IN MEN

Osteoporosis occurs in men, but it has been less well studied in men than in women. The principal differences between men and women are as follows:

- Men sustain limb fractures more commonly than women do before the age of 50 y, but then fractures in women become more prevalent (*129*).
- Similarly, men sustain vertebral fractures more commonly than women do before the age of 50 y. These differences have been attributed, with limited evidence, to risk taking in men, chiefly in contact sports. After the age of 70 y, the fracture incidence in men parallels that in women but with about a 2-decade time lag (*130,131*).
- Men tend to lose bone with age in parallel with women, although without the accelerated phase in women after menopause (*130–132*).
- Age-related bone loss differs in men and women in that the thinning of the endocortex observed in the latter does not occur in the former (*133*).
- The data relating age to fracture risk in men are nearly all derived from studies of cross-sectional, not prospective, design (*21–23,133*).
- There are conflicting data about the equality of fracture risk in both sexes at a given BMD (*130,132–135*).
- The DXA data do not take into account differences in bone size between men and women because of the use of areal density as noted above.
- More men die of the complications of osteoporosis, such as hip fracture, than die of prostate cancer, and osteoporosis tends to be more lethal to older men than to women of the same age (*136*).
- Secondary causes of osteoporosis in men (40%–70% of cases) are principally low serum testosterone concentrations, glucocorticoid administration, and alcohol abuse (*137*).

Few guidelines specifically address male osteoporosis, but those that do suggest BMD testing after age 70 y (*7*) or 65 y (*109*) or after age 50 y in the presence of 1 major or 2 minor risk factors (*109*).

AN INTERNATIONAL PERSPECTIVE

The nuclear medicine community is a global one, and the Society of Nuclear Medicine has both an international purview and an international membership. Therefore, it is appropriate to reflect that no review such as this should narrowly focus on North American practice alone. The available diagnostic technologies, to say nothing of treatments, differ between nations just as do fracture rates, as has been noted.

Each country must arrive at its own solution in addressing competing social priorities, the willingness of patients and society to pay, and resource availability—as noted above with respect to guideline development. Thus cost-utility analyses will encompass both cultural and fiscal elements, as well as the priorities of the body politic in each nation.

It is important to realize that no existing guidelines or strategies for either diagnosis or treatment have been subjected to prospective testing, much less validated in practice. A distinction is being made here between the pivotal controlled trials of drug treatments and population outcome studies of guideline implementation in a society at large. Moreover, as noted above, the guidelines of the U.S. National Osteoporosis Foundation are seen in Europe as too inclusive in their recommended approach to prevention, diagnosis, and treatment based on readings of the evidence,

social priority setting, and expected outcomes. There is not and cannot yet be a global threshold above which it is cost-effective to treat osteoporosis with pharmacologic agents.

THE SEMIOTICS OF OSTEOPOROSIS

A tension exists between use of a formalism such as the WHO classification of people as having normal, osteopenic, or osteoporotic bone densities, as described above (*3*), and the view that this represents a gratuitous "medicalization" of either menopause or aging (*9*). In particular, objections have been voiced to attaching a diagnostic label of "osteopenia" to a group of people, many of whom simply have a BMD in the lower region of the normal gaussian distribution of BMD in any population. This conviction has been reinforced by public suspicion, to say nothing of skepticism, of the pharmaceutical–industrial superstructure constructed around the understandable fear of fractures by aging individuals. Certainly, the act of putting a label on patients with subtle degrees of low BMD (not necessarily representing bone loss) has sometimes led to pharmacologic interventions long before age as a cofactor begins to make fracture risk tangible in most patients. This will be particularly unfortunate until more is known of the long-term safety of some of the drugs currently used to treat osteoporosis.

At the same time, there is the paradox that has already been noted that many people with fractures are not being treated despite evidence, in the form of fractures, that they already have a potentially lethal disease.

As clinicians, we have to resolve the dilemma represented by this debate in dealing with individual patients. People provide their own imperative. We have to rely on our judgment to walk the fine line between medical care and clinical arrogance. There is justifiable apprehension by older people who wish to minimize the adverse effects of osteoporosis they may have seen in their ancestors, and this apprehension must be balanced by any temptation on our part to act in a manner that adds to the ranks of the "worried well."

From this perspective, risk-based assessments as described above (*64–66*), rather than the use of debatable diagnostic labels, are welcome and may take on a particular importance.

THE FUTURE

For an international society such as the Society of Nuclear Medicine, it is important to recognize that there are national and regional implications in health care policy development in relation to diseases such as osteoporosis. Not only are there regional differences in disease, but cost-utility analyses in different societies and cultures will show differences based partly on social values and partly on the economic resources available to a society (*97,104*). There is a need for such issues to be tabled and debated.

Within the professional lifetime of many still in practice, osteoporosis has changed both conceptually and in practice. It has gone from being considered simply an inevitable aspect of the aging process to being recognized as a disease that is treatable and that, if left untreated, has potentially catastrophic consequences for the polity of health care, to say nothing of the individual. While we continue to debate and improve the semiotics of osteoporosis, the personal, social, and economic impacts of the disease cannot be dismissed.

At the same time, the diagnosis of osteoporosis has now moved into a multidisciplinary mode that still involves quantitative physiologic and pathophysiologic considerations. As the field increasingly comes to combine quantitative measurements of bone along with morphometric image analysis (not unlike other developments in nuclear medicine), it remains for us individually, collectively, and as a society to determine our roles in this important, fascinating, and evolving disease context.

(Footnote: In 2004, the U.S. Surgeon General published a report entitled "Bone Health and Osteoporosis," which is a useful resource to recommend for patients (*138*).)

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