Osteoporosis, a disease characterized by low bone strength and fractures that occur with very low-impact loads, has experienced many changes over the past 20 years and we should expect to see many more in the future. Prior to 1990, there was little activity in the field: although there were some small studies with sodium fluoride, they set the field back because these compounds improved bone mass but increased bone fragility and fractures. While osteoporosis, or bone fragility, was generally accepted to be part of the normal process of ageing in post-menopausal women, an osteoporotic fracture diagnosed the disease, unfortunately at a very advanced stage. Until the development of DPA followed by dual-energy X-ray absorptiometry (DEXA), there was no method to determine an individual’s risk of an osteoporotic fracture before the event. However, in 1992, T-scores (S.D.’s above and below peak bone mass) became a way to identify individuals who would, over time, be at increased risk of osteoporotic fractures [1]. This ability to identify individuals at risk for fractures prior to their occurrence by DEXA, coupled in 1990 with the first studies to find a reduction in incident vertebral fractures with the bisphosphonate etidronate, administered for 2 weeks every 3 months, followed by the approval of the bisphosphonate alendronate in the USA in 1995, really jump-started the field. Post- and pre-menopausal women and men obtained BMD scans, and, based on a T-score of −1 or below at the lumbar spine or hip, were started on this anti-resorptive agent indefinitely. Over time, other bisphosphonates were approved, initially daily treatment, then weekly, then monthly, followed by i.v. therapies, first every 3 months and now annually [2]. The past decade also saw the approval of the first ‘anabolic’ or bone-building agent that could increase bone strength by increasing both bone formation and bone resorption. The concept of an anabolic agent that could improve bone strength through increasing remodelling was difficult for the medical community to understand; we learned that the bone matrix is rich in growth factors for osteoblasts including Transforming Growth Factor-β1, Insulin Growth Factor-1 and Fibroblast Growth Factor-2 [3, 4]. The anabolic agent teriparatide allowed bone strength to increase by adding bone to existing trabeculae [3]. However, with the discontinuation of teriparatide, the new bone would be rapidly lost; the addition of an anti-resorptive agent maintained or even increased BMD [5].

The addition of an anabolic agent as a treatment for osteoporosis came at nearly the same time as the Women’s Health Initiative Study in the USA reported that HRT, while effective in reducing hip fractures and gastrointestinal cancer, had risks of cardiovascular events (MIs, strokes, deep venous thrombosis) that outweighed the benefits [6]. This dramatically changed how physicians treated post-menopausal women, especially in the prevention of oestrogen-deficient bone loss in early menopause. However, the number of new, generally non-hormonal medications to treat or prevent osteoporosis kept clinicians busy learning the biology of bone metabolism, and most became very good at identifying and prescribing for patients who should be treated for osteoporosis. However, other than the one anabolic agent, teriparatide, there was no information on how long to treat with anti-resorptive agents or information about drug holidays.

The Fracture Intervention Trial Long-term Extension (FLEX) study, sponsored by Merck, determined that women with osteopenia, and a hip T-score above −3.5, treated with alendronate for ~4.5 years, retained the majority of the bone gained at the hip and spine and showed no significant difference in morphometric fractures 5 years after discontinuation compared with subjects who continued treatment [7]. This information suggested to clinicians that after 5 years a potent anti-resorptive agent could be discontinued, but no guidelines were produced on how to monitor these subjects after therapy was discontinued: this has been left to clinicians to figure out.

In the past 3 years, quite unexpectedly, a number of series of cases of subtrochanteric or atypical fractures have been reported in women treated with bisphosphonates for a number of years. The reports from multiple centres are strikingly similar. The American Society of Bone and Mineral Research convened a task force to investigate the problem [8] and the Food and Drug Administration made recommendations. One of the major risk factors appears to be the length of time a patient has taken the bisphophonate. While pharmaceutical manufacturers were successful in convincing clinicians that these medications would improve patients’ bone strength, no guidance was provided on the length of time that the medication should be prescribed. The Phase III studies carried out to seek FDA approval of the bisphosphonates were only 3 years in duration. However, many of the patients’ subtrochanteric fractures had been
treated with these medications for much longer. So we have learnt a lesson in the treatment of osteoporosis: 3 years is effective, and much longer might cause some harm. This story is not finished.

The use of the T-score to identify patients who might be at risk for osteoporotic fractures, and using a T-score of −1 or less as a threshold to treat patients with bone-active medications, was not satisfying. For a woman at menopause, a T-score of −1 might just reflect her peak bone mass. At her young age, nearly 20 years before, she would be at risk of osteoporotic fractures; medication to prevent osteoporosis might not be worthwhile. The development of the Fracture Assessment Tool (FRAX) has greatly aided clinicians in determining the risk of osteoporotic fracture in individual patients [9]. By sitting with a patient and identifying risk factors on the computer, adding the hip BMD, and then being presented with the 10-year risk of a hip fracture and major osteoporotic fracture, we can identify the most appropriate patients to treat to prevent osteoporotic fractures. The fracture risk thresholds for treatment vary by country; however, the most significant risk factor is age, and with use of the FRAX to identify subjects to treat, we are treating fewer women around the age of menopause.

The future is bright for the development of osteoporosis treatments. New anti-resorptive therapies including denosumab and odanacatib (still in development), to name a few, are potent but have a much shorter half-life in the bone. Denosumab, an inhibitor of Receptor Activator of NF-B Ligand, is given by s.c. injection every 6 months [10]. Odanacatib, an anti-resorptive agent that inhibits the enzyme cathepsin K, a collagenolytic, is given by mouth daily in clinical trials [11]. A new anabolic agent, also in development, inhibits sclerostin, synthesized primarily in osteocyte terminally differentiated osteoblast cells within the bone matrix, which connect to each other through dendritic processes and to the bone surface. Sclerostin is produced by osteocytes and released into the bone marrow, where it inhibits the maturation of osteoblasts. In rodents, an inhibitor of sclerostin increases bone formation dramatically and has been able to rapidly restore peak bone mass [12]. Phase II clinical trials are ongoing. However, as with teriparatide, the new bone mass gained from inhibition of sclerostin is lost rapidly, so either maintenance treatment or prolonged use of an anti-resorptive agent will be needed. Agents that can direct mesenchymal stem cells to move to the bone surface and differentiate into osteoblasts to form bone are also in development [13]. This type of therapy may be useful in accelerating fracture healing.

Since 1995, with the approval of alendronate for treatment and prevention of osteoporosis, and the availability of DEXA to determine risk of osteoporosis, clinicians have been busy diagnosing and treating this disease. Today, we have many highly effective agents to improve bone strength, some by reducing remodelling and others by increasing it. We have increased our bone cell vocabulary to include osteoclasts, osteoblasts and even osteocytes.

We also know that these cells work together to build and maintain a strong skeleton. In the next few years, we will improve our understanding of osteoporosis and bone fragility, and hopefully refine the length of time we use bone active agents to maximize efficacy and reduce toxicity. However, while medications can improve bone strength, a patient generally has to fail to suffer a hip fracture. Clinicians, almost as a reflex, institute medications to treat osteoporosis, and fail to do an assessment of a patient’s risk of falling. A thorough evaluation for osteoporosis and fracture risk includes: a review of the patient’s medications for sedatives/hypnotics that impair balance and increase fall risk; a physical examination to determine muscle strength and balance; and a review of laboratory tests including haemoglobin, haematocrit and electrolytes. Lastly, a review of the home should be done to determine whether there is anything that could increase fall risk. Preventing a fall through the use of an assistive device like a cane or a walker may do as much as any medication [14, 15].

Going forward, this author would like to believe clinicians will be more thorough in their assessment of fracture risk both with FRAX and an assessment of fall risk, and interventions may be both pharmacological and non-pharmacological. Osteoporosis is a chronic degenerative disease, and screening is recommended at the age of 60 years with risk factors and at the age of 65 years without. Since most women live into the mid-eighties, clinicians will be monitoring and treating their bone health for 25 years. The unmet need is to understand how to monitor bone strength so that clinicians know when to start, stop and reinstitute medications to maintain skeletal health. We have come a long way, but we have much left to do.

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Nancy E. Lane¹

¹Department of Medicine, University of California at Davis School of Medicine, Burlingame, CA, USA

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Correspondence to: Nancy E. Lane, Department of Medicine, University of California at Davis School of Medicine, PO Box 589, Burlingame, CA 94011, USA.

E-mail: nelane@ucdavis.edu
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