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Editorial

Osteoporosis-2044

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Why 2044? Because it is 50 years hence, and with a decimal numbering system and five-fingered hands, 50 is a number we celebrate. The half century mark is a significant number for biological reasons as well. Dent was the first to comment that, in certain major respects, osteoporosis is a pediatric disease that commonly takes until old age to express itself [1]. Since 50 is less than two-thirds of the human lifespan, most of the individuals who will have osteoporosis in 2044 are alive today, fully grown, with as much bone as they will ever have, and well settled into the life patterns that will at least partially influence whether they will later express this disorder.

Osteoporosis is a disease of many causes and expressions, and the secular unfolding of each is not likely to be the same over the next 50 years. Focusing mainly on fragility fractures of the old elderly, one can discern three groups of forces likely to influence the character and prevalence of this problem in 2044. The first group is demographic, and includes not only the obvious change in the age distribution of the population, but changes in age-specific prevalence as well. Age distribution can be reckoned with some certainty, especially in the industrialized populations, while age-specific incidence requires extrapolation from current trends. The second group is made up of the forces of medical progress – progress in reversing the fracture syndrome, in treating the predisposing bony fragility, and in preventing development of that fragility. These forces, too, must be extrapolated. The third group of influences is extrinsic and includes social and economic forces that we in biomedicine generally ignore, mainly, I suspect, because we sense we cannot do anything about them. It is my conviction that the extrinsic forces will prove to have more influence on Osteoporosis-2044 than will all the others combined.

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Demographic and Lifestyle Factors

Since those who will be 85 in 2044 are 35 today, we have a solid basis for estimating actual numbers of 85-year-olds 50 years from now. In the United States the population of over-65s will increase to 2.5 times its present numbers, while the population 85 and older will increase by nearly 6-fold [2]. Additionally, the *proportion* of the elderly in the population of the industrialized nations has been rising for a century. With low birth rates in many of these countries, the distribution will continue to become more and more top-heavy. In the United States today there are slightly more than 4 wage earners for every retiree. That ratio will drop to slightly more than 2 to 1 by 2044 [2]. This is an important issue because the burden of osteoporosis costs and care will have to be borne by a progressively smaller proportion of the population.

Age-specific incidence of most fractures in the old elderly has also been increasing since World War II in most of the industrialized nations, although there is a suggestion that this change is now levelling off [3]. Moreover, orthopedic surgeons note that fracture comminution is increasing in parallel with age-specific incidence – a further indication of growing fragility [4]. While the reasons for the increase in age-adjusted fragility are not known with certainty, the hypothesis most consistent with the available data, and best accepted by most fracture epidemiologists, is that it is the decrease in physical activity that has occurred since World War II which is responsible [3–5]. Decreased

loading would certainly reduce bone mass, and might influence repair of fatigue damage as well, thereby making bones more fragile for two reasons.

Thus, other things being equal, the numbers of fragility fractures and of patients with osteoporosis, particularly over 80 years of age, will certainly increase by several-fold over the next 50 years. Will other things be equal? Almost certainly not. Medical progress may be presumed to alter the expression of these trends. That progress can be dealt with under three headings: treatment of expressed osteoporosis, reversal of unexpressed osteoporosis, and prevention of skeletal fragility.

Treatment of Expressed Osteoporosis

Obviously treatment of expressed osteoporosis will not alter prevalence of the disorder. It will affect only the quality of life of patients with fractures. Although a much less grim prospect, treatment of expressed osteoporosis is like treatment of paralytic poliomyelitis or end-stage renal disease. It is what the late Lewis Thomas called 'half-way technology' [6]. I am confident that we will still be using such treatments in 2044, and it is likely that they will continue to engage a great deal of our attention and consume a substantial portion of the resources devoted to osteoporosis, as does all half-way technology. But this expenditure is unlikely to have much impact on the overall problem. Furthermore, such treatments tend to be inherently expensive and, in an international climate concerned with controlling health costs, they may not be widely deployed. Nevertheless, modest improvement in treatment of fractures (or of patients with fractures) and in the numbers of agents available for that treatment is likely. In addition to current approved and investigational agents, I expect to see a major role for combination therapy.

Reversal of Fragility, Pre-fracture

Treating the predisposing fragility in order to prevent fracture is a probable and almost certainly necessary development. Necessary, because the seeds for that fragility, *à la* Dent, are already sown for the crop of 2044, and will inexorably come to harvest unless we can intervene effectively. That harvest is simply waiting for the right combination of falls, clumsiness, soft tissue loss, accumulation of microarchitectural damage, and further skeletal weakening from age-related bone loss, to express itself as fractures.

The most promising agents currently able to reverse low bone mass are fluoride and parathyroid hormone (PTH) [7,8]. Neither is an ideal drug. Unless we find less expensive ways to deliver it, PTH is unlikely to be widely used to treat unexpressed osteoporosis. Fluoride offers much more promise in that regard. It is the most potent, clinically applicable osteoblast mitogen we know of, and it does improve axial bone mass, both cortical and trabecular. Whether we will be using either agent to increase bone mass in 2044, or whether we will look back upon them as surrogates or prototypes for new generations of osteogenic agents – what are called generically 'growth factors' – I cannot say. For some of these factors we shall have to find a way to deliver them specifically to the proper tissue target; this is not a trivial issue, but one that is probably solvable.

Prevention of Osteoporotic Fragility

Preventing the fragility in the first place – or reducing its magnitude – is obviously the most attractive strategy. Calcium, vitamin D, gonadal hormones and exercise are well-recognized factors influencing bone mass and age-related bone loss. While there are still several important research questions about their roles and interactions, there is consensus that, fully deployed, they would substantially reduce the prevalence of low bone mass, and thus of fragility fractures [9–12]. So the issue for 2044 is not so much the discovery or development of new preventive measures, as whether and how we shall deploy established measures.

Increasing calcium intake and ensuring vitamin D sufficiency are obvious and necessary steps, particularly during growth when achieving genetically programmed bone mass is still possible. Even in the old elderly, supplemental calcium and vitamin D have been shown to reduce fracture incidence by 20%–40% [10–12]. How much better they might do if started at a younger age, particularly during growth, is unclear. At a population level we shall probably augment calcium intakes by means of a variety of food fortifications, analogous to the control of dental caries by water fluoridation or of endemic goitre by iodination of salt. We are already seeing this happening in the United States. Fortification of orange juice and white bread are examples. If continued as a voluntary matter, such fortification will occur relatively easily. But, if mandated, it will be a contentious and difficult public policy issue, just as was water fluoridation.

Hormone replacement therapy (HRT) at menopause is also a well-recognized, proven strategy. The fracture reduction of menopausal HRT has been estimated at from 30% to 60% [13–15]. Unfortunately, acceptance of HRT is poor, although it may be that newer generation hormone agonists/antagonists such as raloxifene [16] will improve that situation substantially. The decline in testicular function in many men with age, and the adrenopause in both sexes, while less obvious than female menopause, may also contribute in the same general way to the burden of bony fragility in the elderly. All three declines may present attractive opportunities for sex-specific HRT.

Even so, calcium, vitamin D, and gonadal hormones, taken together, are unlikely to prevent much more than half of the problem of skeletal fragility. (Each agency probably does something close to that by itself, but the available data suggest to me that these modalities save

many of the same people.) A part of the reason for less than complete effectiveness is that none of these approaches does much to counter the disuse component of old age fragility or the injury/trauma component of fragility fractures.

Thus, given the increases both in the numbers of elderly and in age-specific fragility, it is likely that real successes in deployment of proven preventive measures will be at least offset, and possibly swamped, by increases in numbers of persons with fragility. The arithmetic is straightforward. If we reduce the incidence of fractures in high-risk elderly by 50% – a remarkable victory, actually – but the size of the group doubles, then absolute numbers of fractures will remain unchanged. And if the at-risk group triples or quadruples (as will happen to the older age cohorts), actual numbers of fractures will increase by 20%–80%.

The most logical way to handle the disuse component of age-related loss is to structure society so that physical work does not decline with age – an unlikely scenario under current conditions. Any medical progress reducing the all-cause infirmity of old age would also help. Alternatively, we might succeed in finding a way to change the set-point of the bone mechanostat. Our current focus on therapies that target either resorption or formation somewhat misses the point. To the extent that such agents work at all, they increase bone mass despite the fact that the mechanostat 'thinks' there is more bone present than is needed. The result is that the bone's own internal control system tries to compensate, i.e., it works against our therapy. We would be better off learning how to control the mechanostat than continuing to bypass it. Is this possible? I think so. We shall first have to find out how it works, and that means developing an adequate model for the intermediary organization of bone. Will we attempt to do so? I do not know, though I suspect we will, once our short-term infatuation with the remodeling therapies cools, and once we focus on prevention instead of treatment.

New Paradigms

One must pause to consider that there is always the chance that our current osteoporosis/bone paradigm will be outmoded by 2044, and that a new biological model, either for the disease or for its treatment, will come along and replace our current way of looking at osteoporosis. By 2044, osteoporosis might be as controllable or uncommon as smallpox or polio. The truly new is never detectable at its inception – only in hindsight – simply because its significance can only be appreciated in light of what it will become [17]. So I am not able credibly to predict in this regard. But I am able to predict something about the deployment of any totally new approach. The time lag between the birth of a new technology and its widespread application, at least over the past 50 years, has been so long that even a magic bullet, emerging unrecognized today, may not be fully deployed by 2044. Pessimistic as that sounds, one need only recall that the birthdate of the age of molecular biology was 1949, with publication by Linus Pauling and his colleagues of the molecular basis of sickle cell anemia [18]. Today, 45 years later, with contemporary research agendas dominated by molecular biology, we are just beginning to contemplate how we might apply that watershed discovery of Pauling's to treat actual patients with sickle cell anemia, and we have yet to deploy any clinically practicable solution to the problem.

External Forces

The foregoing extrapolations from current demographic trends and biomedical progress assume little change in external economic and social forces. That is an improbable assumption. The most important of the external forces is the availability of energy, which drives the economies of all the capitalist, industrialized nations. A moment's reflection helps us to realize that the underpinning of the entire process of civilization, from prehistory to the present, has been access to, and control of, energy. Per capita energy consumption has increased more or less steadily throughout the last 10 000–12 000 years, from something like 10.5–12.5 MJ/day in the hunter-gatherer state to something close to 1250 MJ/day in the United States today. The rise or development of nations and societies has been literally fuelled by a strictly parallel rise in energy consumption. The doubling time for energy consumption has been getting shorter and shorter: the last was only 20 years. It is obvious that the trend cannot continue indefinitely, but what is little appreciated is that the per capita energy peak will not occur at some far-off, distant time but, instead, precisely during this next 50 years. It is not just that growth will slow. Per capita energy utilization will actually begin to decline.

Our world has been built on consumption of fossil fuels, and while coal is still present in abundance, world petroleum reserves are declining every year [19], a situation aggravated by world population growth and, even more importantly, by increasing per capita utilization of energy. (World energy consumption doubled from the mid 1960s to the mid 1980s, partly because of population growth. But in the United States – the world leader in consumption – actual per capita consumption itself doubled during the same period.) Alternative energy sources are not being developed fast enough to take up the slack. And fusion power is a long way off. (The most optimistic estimates put the first operational fusion reactor coming on line in 2035, just 9 years short of 2044, and well past the peak of petroleum availability.)

When energy supplies become seriously limiting, the impact on the economies of the industrialized nations will be catastrophic, on a scale vastly greater than the current turmoil in the former Eastern Bloc nations. Economies dependent upon growth will inevitably falter and collapse. It may be hard today to credit that such an

energy crisis will happen at all, with current petroleum prices stable, or even falling. But we shall surely feel the pinch no later than 20–30 years from now – well before 2044. What will this change mean for a disease such as osteoporosis? How important in 1994 is osteoporosis in Bosnia?

It would take volumes even to list and describe all of the ramifications of the forthcoming energy crisis, but some few seem clear. First it is helpful to note that transport is the largest component of United States energy consumption, and that, together with electrical power generation, it accounts for more than half our total. Inevitably, therefore, our contemporary automobile-centred economy, with all of its consequences (suburban sprawl, the decay of public transport, the paving of the planet, to mention only a few), will collapse. It will also be looked back on as a shameful, profligate waste, a squandering of our children's inheritance.

With less energy available, we shall all work harder and exercise more. (That at least will be good for our bones.) As the standard of living declines, lifespan may be shorter as well. (That, in its way, will decrease the osteoporosis problem also.) There will be less money for medical research then, and for medical treatment as well, just as there will be for everything else. The good times are now.

Even more sinister are social developments, shifts in our attitudes toward the elderly and toward dying, which will be given added impetus by the combination of economic strain and the rise in the numbers of dependent elderly. The current rise in 'granny bashing', the increasing legal tolerance of euthanasia in The Netherlands, the growth of the Hemlock Society in the United States, the high popular approval rating of America's own 'Dr Death', are all indications of a trend: the unthinkable is increasingly being thought. Attitudes toward euthanasia are now focused on self-determination, on the right of an individual to end an irreversibly painful life. But it may not be too much of a stretch of the imagination to envision those forces shifting to societal termination of irreversibly costly or burdensome lives. Repugnant as that may seem to us – certainly to me and to the Judaeo-Christian religious tradition that has shaped me – it is vital that we identify and understand the forces at work in this situation.

If public policy toward euthanasia shifts to any appreciable extent, the osteoporosis problem will decline. When our children, caught in economic collapse and stuck with paying for our hip fractures, fully realize that their own straitened circumstances are due to our heedless folly, their attitudes towards us are likely to be harsh. The aphorism that a society is judged by how it treats its most vulnerable members is, at least in part, an aphorism of affluence. Nevertheless, in mitigation of the bleakness of this prospect, I must note that humans cared for one another before they became affluent, and that they do so today even in the poorest communities – at least so long as they are part of stable societies. Thus I do not predict a universal decline into brutishness. Nevertheless, the relative proportions of dependents and of care-givers will be unprecedented, and the social disruption of the shift to a lower standard of living will make the transition exceedingly difficult.

Summary

It is likely that by 2044 biomedical and public health forces will be able to control bony fragility to a substantially greater degree than we have succeeded in doing today, but that demographic and lifestyle forces already at work will offset those gains, perhaps substantially. On the other hand, economic and social forces outside of our control will decrease the prevalence of skeletal fragility – harshly, I fear – either by strengthening old bones the hard way, or by decreasing the numbers of the elderly, or both. The final outcome will be the algebraic sum of the effects of these countervailing forces, which is impossible to estimate with any assurance. My guess is that osteoporosis will be less of a problem in 2044, though, unfortunately, for the wrong reasons.

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