loading stress to bone, such as aerobic dancing or jogging, are more effective than activities such as swimming, that do not. These short-term increases in bone density were of the same magnitude as those found after successful estrogen therapy. For example, in five recent studies, the rate of change in bone mass at various sites in postmenopausal women in an exercise program was about +3 percent per year, while it was about −3 percent per year in the sedentary control group.

Although these data are encouraging, three caveats should be mentioned. First, the rates of change in bone density, based on a relatively short period of observation (usually 1–2 years), may not be maintained for longer periods. Second, treatment and control groups have not always been randomly assigned and, therefore, other factors besides the effect of exercise may have been operating. Third, the amount of exercise required to achieve these rates requires rather intense weight-bearing exercises for 15–30 minutes a day several times a week, and this may not be appropriate for all women, some of whom may have other significant health problems, such as osteoarthritis of the knee or hip. Even so, the early results are extremely promising, and need to be extended and better quantified. Considering the other health benefits of increased exercise, however, including cardiovascular fitness, it is not too early to suggest that the entire adult population should increase its physical activity. Those at risk for osteoporosis should consider discussing with their physician the advisability of enrolling in a regular fitness training program.

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Panel Session: Nutrition/Exercise

The Calcium Controversy: Finding a Middle Ground Between the Extremes

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Synopsis

Involutional bone loss, and the fracture syndromes that are designated "osteoporosis," are multifactorial phenomena. Gonadal hormone deficiency, inadequate exercise, and a multitude of lifestyle factors are involved in their pathogenesis. Calcium is important during growth, and probably up to about age 35, when peak bone mass is finally achieved. Recent controversy concerning the role of calcium in the middle-aged and elderly, arising out of population studies showing sometimes only weak calcium effects, can be resolved by recognizing the multifactorial character of involutional bone loss, and by careful attention to such details as national differences in habitual calcium intakes. Thus interpreted, metabolic, epidemiologic, and intervention studies are internally consistent, and indicate that inadequate calcium intake also makes an important contribution to involutional bone loss.

THE 1984 NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT CONFERENCE proposed figures of 1,000 milligrams (mg) per day for estrogen-replete, perimenopausal women, and 1,500 mg per day for estrogen-deprived women remain the best estimates for recommended calcium intake. Such intakes are both safe and natural. While some people can adapt to intakes substantially below those levels, not all persons can, particularly many middle-aged women and the elderly of both sexes. Since we cannot

now identify those who are calcium-deficient from those who are not, it makes good sense to ensure a generous calcium intake for the entire adult population. Several recent reviews have exhaustively treated certain topics covered in this paper (*1,2*). Literature citations in this article will be to those reviews where appropriate.

The role of calcium in osteoporosis has undergone surprisingly wild swings in both public and scientific opinion in the past 25 years. In the mid-1960s, the major textbooks of medicine either ignored calcium entirely or asserted that it was of no importance in the genesis or prevention of osteoporosis (*3,4*). But a growing body of evidence forced a change in those views, and culminated in what has been termed the "calcium craze" from 1982 throught 1986 (*5*). Calcium supplement sales rose from less than $20 million per year in 1982 to over $120 million in 1986, and the public was confronted with a barrage of advertising claims and information about calcium in the popular media (*5*). In the past 1–2 years, perhaps in part due to the promotional excesses of the pharmaceutical industry, there has been a swing of scientific opinion in the other direction. For example, one major medical journal has recently permitted its editorial pages to be used to deprecate the role of calcium in adult bone health (*6*). Whatever may be the reasons for these conflicting currents of opinion, in this paper I attempt to place calcium intake in an appropriate perspective and to outline a prudent course for the American public, located somewhere between the extreme views that have characterized the past few years.

Background

Calcium deficiency in animals. Over the past 60 years, many experiments have shown that laboratory animals placed on low-calcium diets develop osteoporosis. (*2*). It is easier to produce the disorder in some species than others, cats being particularly sensitive, but the condition has also been produced in dogs, rats, and mice. Calcium-deficiency osteoporosis in cats constitutes a classical type of nutritional deficiency experiment: removal of an essential nutrient creates the disorder in a short time, and then its restoration leads to substantial healing. In fact, calcium-deficiency osteoporosis is the only laboratory model of osteoporosis available. By contrast, efforts over many years to produce an estrogen-deficiency model, comparable to human menopausal bone loss, have been largely unsuccessful.

The bone loss of calcium deficiency is mediated by parathyroid hormone, which stimulates bone resorption in an attempt to maintain the calcium level of extracellular fluid in the face of obligatory losses which occur in excess of absorbed intake. The bone loss of low calcium intake can be prevented by prior parathyroidectomy, although at the cost of unacceptable hypocalcemia. Most animals, having relatively higher calcium intakes than humans, do not develop the severe hypocalcemia after parathyroidectomy that characterizes human hypoparathyroidism. Instead, they mainly lose the ability to regulate calcium levels in the extracellular fluid and have uncontrolled swings, both up and down.

Primitive human calcium intake. The level of calcium intake of contemporary humans is of very recent origin when viewed against an evolutionary time frame. Efforts to reconstruct the primitive intake of many nutrients, calcium included, have been undertaken to give clues about the kind of diet to which our physiology has become adapted over the millenia of evolution. Eaton and Konner (*7*) published analyses of the diets of contemporary hunter-gatherers, and showed that their mean year-round calcium intake is about 1,600 milligrams (mg) per day. Eaton (*8*) recently raised that estimate, and now suggests that the typical intake is closer to 1,900–2,000 mg per day. This is from three to four times the mean intake of contemporary middle-aged American women (*1*). Further, this higher level of intake is much more typical of calcium intakes of most other omnivorous mammalian species. In fact, as has been noted elsewhere, (*9*), after correcting for differences in body size, the human Recommended Daily Allowance (RDA) for calcium is only about one-fifth that of domestic livestock and household companion animals.

Adaptation. That cats develop osteoporosis when calcium intake is restricted, and that the primitive human calcium intake appears to have been considerably higher than our own, do not prove that human osteoporosis is a calcium-deficiency disorder. But these facts do show what calcium deficiency would be predicted to do to human bone if intakes fell to the level of true deficiency and, together with the very ubiquity of osteoporosis, they do at least force serious attention to the question of whether contemporary dietary calcium intakes may be deficient.

Many humans can build a functionally adequate skeleton on intakes that might seem to us to be inadequate (*10*). Thus, it follows that humans have an ability to adapt to low calcium intakes. Indeed, it could hardly have been otherwise, even under primitive conditions, for there must have been periods when

calcium-rich foods were in short supply. However, the fact of adaptation does not eliminate the problem of evaluating the association of calcium intake and osteoporosis, because there is an abundance of evidence that, while some persons can adapt, not all can do so (*11*). Furthermore, as is well recognized, the ability to adapt changes with age and hormonal status (*1,2*). Finally, osteoporosis may be concentrated in that subset of the population who have the poorest ability to adapt, and who ingest habitually low amounts, as well. In support of this possibility, essentially all reports of calcium intake in patients with osteoporosis have shown lower intakes than in age-matched controls (*1*).

Distribution of actual calcium intakes. The two National Health and Nutrition Examination Surveys (*12, 13*), covering 1971–80, both showed that calcium intake in U.S. women is typically 40–50 percent lower than in men, that 75–80 percent of mature women regularly ingest less than the 1980 RDA for calcium (800 mg), and that, even worse, 25 percent of the women in the United States regularly ingest less than 300 mg per day. This latter group is of particular importance. Given the other components of a typical modern diet, an intake as low as 300 mg is beyond the capacity of most women to adapt (*11*). Hence, virtually all women in this lowest quartile of intakes must be losing bone.

Involutional bone loss: a multifactorial disorder. Most workers in the field would agree that involutional bone loss is a multifactorial affair, just as is anemia. Bone health can be thought of as a chain, whose links collectively determine its overall strength. Calcium, gonadal hormones, and exercise can be thought of as independent, important links in the chain of bone mass (*2,14,15*). Smoking, alcohol abuse, and qualitative changes in the bony material probably also play a role (*16, 17*). Finally, there is suggestive, though not strong, evidence that the vitamin D family of hormones (apart from their effect on calcium homeostasis) and various trace metals also contribute to skeletal integrity (*2*). As with anemia, where iron, B_{12}, folacin, hemopoietin, and a responsive marrow are all essential for hemoglobin production, supplying more of one link that is not actually limiting (even if deficient) will have little or no effect. This conceptual framework is helpful because evaluation of published studies using either bone strength and fragility or bone mass as the end point will inevitably be influenced by the weakest link in the chain of each individual's bone health. Unless a study population is selected for its calcium-deficiency status, it will be difficult to discern the effect of calcium intake. All of the relevant co-variables must be factored into such an evaluation.

The purpose of this paper is to review the evidence relating to only one of the links in the chain of bone health—calcium nutrition.

Calcium and Bone Health

If, as has been asserted previously, calcium is an important link in the chain of bone health, then one would predict that persons having habitually high calcium intakes would have greater bone mass and strength than would persons with habitually low intakes. Further, one would predict that persons with high intakes would lose bone less rapidly than persons with low intakes, at least if the intakes were low in the sense that they were below an individual's requirement. Finally, one would predict that metabolic balance studies would elucidate the quantitative level of the requirement, and show that persons ingesting intakes below that level are in negative calcium balance, whereas persons at or above that level would be in equilibrium or even positive balance. A large number of studies have investigated these issues, and I will briefly review them.

Metabolic studies. Balance studies have been a classical way of determining nutrient requirements. Current estimates of calcium requirements arise largely from studies done many years ago in healthy young adults. These studies showed that the mean requirement for maintenance of equilibrium was in the range of 450–600 mg per day (*1,2,18*). After making allowances for individual variation in requirements, these data have been the basis for setting the RDA in the United States at 800 mg per day (*19*). This value, as for all RDAs, is designed to be somewhere above the 95th percentile of individual requirements. As has been extensively discussed elsewhere (*1, 2*), the problem with this approach is that at the time these nutritional studies were being performed, researchers did not recognize that adults in the third decade were still forming bone. Hence, an intake just sufficient to maintain equilibrium in them could not at the same time be sufficient to maintain *positive* balance, which is required during a period of growth. Thus, a good case can now be made for maintaining the 1,200 mg RDA set for adolescence until age 30.

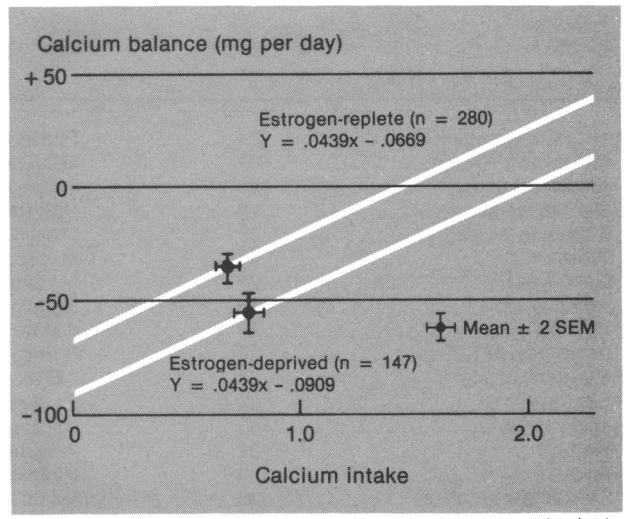
The 1980 RDA further assumed that 800 mg per day was adequate for perimenopausal women as well as for younger persons, but until comparatively recently, no studies of calcium requirements in middle-aged women had been performed. Recent stu-

dies of middle-aged women have yielded mean requirements above 800 mg per day. The largest of these studies, from our Hard Tissue Research Center at Creighton (*20*), showed highly significant linear correlations between calcium intake and calcium balance for both estrogen-replete and estrogen-deprived postmenopausal women, with the two regression lines being significantly different from one another, and the line for the estrogen-deprived group being displaced downward (in a negative balance direction) by about 24 mg per day at all calcium intake levels. Estimates of the mean requirement for the estrogen-replete group were close to 1,000 mg per day, and for the estrogen-deprived, 1,500 mg per day. We have now greatly augmented that experience (R.P. Heaney and R.R. Recker, unpublished observations), and the figure shows the regressions for our current data set, consisting of 280 studies in estrogen-replete women and 147 studies in estrogen-deprived women. The two lines, as before, are significantly different from one another ($P < .01$), but their slopes are essentially identical. This indicates that both groups exhibit the same positive relationship between level of intake and level of balance, though they operate around different set-points.

These data reflect what would be predicted if calcium were a nutrient important for bone health, namely that persons with intakes below their requirement would be in negative balance (would be losing bone), whereas persons with higher intakes would be in calcium equilibrium or positive balance. One would have predicted that the lines relating balance to intake would be curved, rather than linear, with the slope becoming more flat at higher intake levels. But attempts to fit our data to a variety of curvilinear models have failed to improve the fit beyond what we can achieve with a linear model; and since we have a substantial number of studies performed at intakes in the range of 1,500–2,000 mg per day, we conclude that the lines, as drawn in the figure, are the best characterization we can now give the data.

As the figure suggests, the intersections of the regression lines with the zero balance line are somewhat higher than our previously published estimates (*20*). These new values may be, in fact, the best estimates we can now make of the mean requirement for middle-aged women. Some of the studies that I shall allude to later would be compatible with that interpretation. Nevertheless, for the moment, the most important conclusion to be drawn from these studies is that there is a clear relationship between intake and balance. This relationship must be considered to be far more certainly established than is its precise position with respect to the coordinates of the system.

Calcium balance as a function of intake



Least = squares fit lines for the registration of calcium balance on calcium intake for both estrogen-replete and estrogen-deprived, normal, middle-aged women (R.P. Heaney and R.R. Recker, unpublished observations. Copyright R.P. Heaney, 1987; used with permission).

Epidemiologic studies. Table 1 lists the 17 studies (*21*–37) that have been published evaluating the relationship between current bone mass and current calcium intake. Eleven of the 17 showed a statistically significant positive association between these two variables ($P < .05$ or better), and 6 failed to find a significant association. None found a negative correlation.

The most striking of these studies was the report by Matkovic et al. (*25*) from Yugoslavia, in which bone mass values in persons from two rural districts were compared. The inhabitants of one district, a goat herding community, regularly consumed milk and cheese, whereas the people in the other district did not. Calcium intake, of course, declined with age, as has been found in most studies; nevertheless, at all ages the calcium intake in the high-calcium district was about twice that of the low-calcium district for both men and women. Bone mass, as assessed by metacarpal radiogrammetry, was higher in the high-calcium district at all ages for men and women. Since the study was cross-sectional, rates of loss cannot be validly inferred. Nevertheless, older persons had less bone mass than younger, and the differences were approximately the same in both the high-calcium and low-calcium districts. This implies that, whereas a high calcium intake supported development of higher peak bone mass, it did not, in itself, prevent involutional bone loss. A typical person who had more bone at the adult peak of about age 35 also appeared to have more bone at ages 75–85. This study has been widely interpreted as indicating the importance of calcium intake in early life.

Table 1. Cross-sectional studies of the relation of current bone mass and current calcium intake

Investigator	Reference No.	Site	Method[1]	Result[2]
Thorangkul et al.	21	Phalanx	RD	+
Smith and Frame	22	Metacarpal	RG	0
Albanese et al.	23	Phalanx	RD	+
Donath et al.	24	Radius	SPA	0
Matkovic et al.	25	Metacarpal	RG	+
Stanton	26	Metacarpal	RG	+
Garn et al.	27	Metacarpal	RG	+/0
Aloia et al.	28	Radius	SPA	0
Pacifici et al.	29	Spine	CT	0
Laval-Jeantet et al.	30	Spine	CT	0
Kanders et al.	31	Spine	DPA	+
Sandler et al.	32	Radius	SPA	+/0
Yano et al.	33	Radius, ulna,calcaneus	SPA	+
Halioua	34	Radius	SPA	+
Sowers et al.	35	Radius	SPA	+/0
Freudenheim et al.	36	Radius	SPA	0
Nordin and Polley	37	Radius	SPA	+

[1]RD = x-ray densitometry; RG = radiogrammetry; SPA = single photon absorptiometry; CT = computed tomography; DPA = dual photon absorptiometry.
[2]+ = statistically significant positive correlation between current bone mass and current calcium intake ($P < .05$ or better); 0 = no statistically significant correlation between these 2 variables; +/0 = study composite: positive result for one bony region or one population subset; no result for another.

The investigators also assessed the relative incidence in the two regions of two putative osteoporotic fractures, the distal forearm—or Colles'—fracture, and the hip fracture. Persons in the high-calcium district had a hip fracture rate of only about one-fourth that of those in the low-calcium district, whereas there was no difference between the Colles' fracture rates in the two regions. This regional difference in skeletal response has been found by other investigators, emphasizing the fact that the skeleton is not behaving as a monolithic unit in response to any of the changes occurring during the involutional period. This fact cannot be emphasized too highly, for there has been a tendency for scientists, like the six Indian blind men "seeing" an elephant for the first time, to assume that one's piece of the reality was adequately representative of the complex whole.

Most of the other cross-sectional studies have shown less striking differences than the Yugoslav study. Several reasons for this can be advanced, although it is not easy to know with certainty the role each may have played in any given investigation. The most important is the fact, already stressed, that involutional bone loss is multifactorial, and any unselected population will contain both people losing bone because their calcium intake is too low to meet their individual needs and people losing bone for one of the other reasons listed earlier. Another explanation, equally obvious, is the difficulty in accurately assessing calcium intake, particularly for large populations in typical field investigations, because of the subjects' difficulty in remembering what was consumed and differences in perceptions about sizes and portions. The Yugoslav study was spared this problem to some extent by major regional restriction in food availability. So, even if there had been systematic errors in assessing calcium intake accurately, these would not have obscured the large difference in intake between the regions.

Another explanation is the fact that obligatory losses of calcium are probably at least as important as intake in determining calcium nutrient status (*37*). Protein and sodium intakes, for example, affect obligatory calcium loss (*1*), and national differences in intake of such nutrients produce large differences in effective calcium requirements between populations. Also of importance is the factor of nontraditional sources of calcium. This is certainly a problem when one compares groups of different national origins and cultures, since the questions about intake that are asked, and the values contained in the diet manuals, often fail to capture or reflect important sources of calcium. For example, Peruvian Indians add a baked, powdered rock (principally calcium carbonate) to cereal gruel (*38*), and Vietnamese consume a liquid prepared by soaking bones in homemade vinegar (*39*). Other examples abound, and we probably have not discovered all of them. Even in First World countries, nontraditional sources present an important pitfall for intake analysis. For example, the crispy tails of fried shrimp and the crunchy epiphyses of fried chicken bones are very rich sources of calci-

Table 2. Longitudinal studies in which rate of change of bone mass was correlated with current calcium intake

Investigator	Reference No.	Site	Method[1]	Result[2]
Garn et al.	42	Spine	X-ray	0
Aloia et al.	28	TBC[3]	NAA	+
Riggs et al.	43	Spine	DPA	0
		Radius	SPA	0
Dawson-Hughes et al.	44	Spine	DPA	+
Nordin and Polley	37	Radius	SPA	+

[1]NAA = total body neutron activation analysis; for other designations, see table 1, footnote 1.
[2]+ = statistically significant positive correlation between rate of change in bone mass over time with current calcium intake ($P < .05$ or better); 0 = no statistically significant correlation between these two variables.
[3]TBC = total body calcium

um, and when explicitly questioned, many people will admit to eating such foods. But the nutrient content of such food types is virtually never included in standard intake assessments. These are items that may not be major sources of calcium for a Western population, but the failure to capture these sources and others like them introduces another component of variation into an already uncertain measurement. Inevitably, therefore, such uncertainties contribute to the difficulty of finding relationships between variables.

Yet another reason for relatively weak relationships is the fact that current bone mass is as strongly determined by prior bone mass as it is by any current practices, dietary or otherwise (*40*). To the extent that prior bone mass was determined by calcium intake earlier in life, then one would not necessarily expect a close correlation between current intake and current mass. Of course, current calcium intake tends to be correlated with prior calcium intake. But once again the substitution of one variable for another lengthens the associative chain, introduces another source of variation, and inevitably weakens the apparent association. Several recent studies have attempted to assess calcium intake early in life; all of them have found a positive association between current bone mass and early calcium intake (*25, 34, 41*). While consistent with the notion that calcium intake is important for bone health, these studies suffer from the manifest problem that, if it is difficult to assess intake yesterday, how much more difficult must it be to assess what it was 40 years ago! Thus, these studies tend to be less compelling than others, even when they are positive. There is a presumption here also, seemingly reasonable, that negative studies of the same sort would be less likely to be published. Thus, one must confront an inevitable publication bias when doing this sort of meta-analysis.

Given all these reasons why an association may appear weak in cross-sectional study, as well as the fact that, even so, most such studies have shown a positive, if sometimes weak, association, it seems clear not only that calcium intake plays a role in bone health, but also that it is operating precisely at intake levels found in studied populations.

Table 2 presents five longitudinal studies (*28, 37, 42–44*) in which rate of change of bone mass over time has been correlated with current calcium intake. While current bone mass can be measured with considerable accuracy by modern techniques, rate of change in bone mass is inherently more uncertain (*45*), because all of the measurement variability of each of the paired measurements used to compute change is loaded onto the usually small value for the difference. Thus it takes either very long time bases (in which case the change has had sufficient time to become large) or very large samples to offset this inherent difficulty. Nevertheless, three of the five longitudinal studies have shown a positive correlation between current calcium intake and current rate of change in bone mass. The others showed no significant correlation. Once again, no study showed a negative correlation.

Clinical trials. Table 3 presents the 10 intervention studies that have been published (*36, 37, 46–53*). Not all have been randomized, controlled trials, but about 80 percent of them have shown a reduction in rate of bone loss in persons with investigator-initiated augmentation of calcium intake. Two of these clinical trials deserve additional attention, principally because of insights which they provide about aspects of skeletal response to altered calcium intake, and because of the pitfalls of interpretation of such studies which they illustrate.

The first is a study recently published by Riis and co-workers (*53*), widely reported in the lay press as showing that calcium was without effect in preven-

Table 3. Clinical trials of rate of bone loss of persons with augmented calcium intake

Investigator	Reference No.	Site	Method[1]	Result[2]
Albanese et al.	46	Phalanx	RD	+
Horsman et al.	47	Metacarpal	RG	+
		Radius	SPA	+
Recker et al.	48	Metacarpal	RG	+
		Radius	SPA	0
Smith et al.	49	Radius	SPA	+
Nilas et al.	50	Radius	SPA	0
Genant et al.	51	Spine	CT	0
Freudenheim et al.	36	Humerus	SPA	+
		Radius	SPA	+
Ettinger et al.	52	Spine	CT	+/0*
Riis et al.	53	Radius	SPA	+/0
		TBC[3]	DPA	+
		Spine	DPA	0
Nordin and Polley	37	Radius	SPA	+

[1]See table 1, footnote 1 for definitions.
[2]+ = statistically significant positive correlation between rate of change in bone mass over time with current calcium intake ($P < .05$ or better); 0 = no statistically significant correlation between these two variables.
[3]TBC = total body calcium.
*See table 1, footnote 2.

tion of early postmenopausal bone loss. In this study a group of 60 early postmenopausal, estrogen-deprived women were randomized into three treatment groups, one receiving estrogen, one a 2,000 mg calcium supplement, and a third a placebo. Bone mass was measured in four ways (two sites on the forearm, at the spine, and as total body bone mineral). Estrogen was found to protect against age-related bone loss over a 2-year treatment period at all four measurement sites. This finding, of course, has been reported many times before (*15*), and was to be expected. It served as a kind of reference point for the placebo and calcium-supplemented groups. The placebo group, by contrast, showed the now familiar loss of bone over the 2 years of observation at most of the sites. The calcium-supplemented women showed effects intermediate between the placebo and the estrogen-treated subjects at both the diaphyseal site on the forearm and the total body bone mineral, but results were not different from the placebo at the spine and wrist sites. The authors concluded that extra calcium was not a satisfactory substitute for estrogen in protecting against postmenopausal bone loss. If they had treated "...estrogen-deprived, but relatively calcium-replete women," one could hardly disagree. For what has been lost sight of in most of the analyses of this paper is that these Danish women had a high average baseline calcium intake, i.e., just under 1,000 mg per day. Thus, while estrogen-deprived, they would have been considered to be closer to calcium-replete, at least by American standards (where women in this age range have average intakes of about 500 mg per day). Thus, this was a group that, because of national dietary differences, had been inadvertently selected to contain few women with inadequate calcium intakes. One might have predicted that they would have shown no response to ingestion of still more calcium. For that reason it is particularly significant that additional calcium in this study *was* able to reduce bone loss relative to the placebo-treated women, both for the diaphyseal forearm site and for total body bone mineral.

Thus, rather than showing that calcium was without effect, this study clearly demonstrates that a mean intake of 1,000 mg of calcium per day is not high enough to produce the full protective effect potentially available from calcium. It is, therefore, consistent with the metabolic balance studies described earlier in which intake requirements for middle-aged women were estimated to be substantially above 1,000 mg per day.

A second conclusion that is strongly suggested by this study is that, even under conditions of high calcium intake, some bone loss still occurs during the period of estrogen withdrawal immediately following menopause, and the degree of suppressibility of this bone loss by calcium is both limited in degree and not uniformly distributed over the skeleton. However, this observation is not original, having been demonstrated in an earlier study from our laboratory (*48*). In our earlier study, with a very similar design, we noted, as did the Danish workers 10 years later, that estrogen supplementation of early postmenopausal women completely prevented bone loss over a 2-year

period both at a diaphyseal bone site and at the metaphyseal site at the wrist. By contrast, a calcium intake of 1,500 mg per day was able to block calcium loss *only* at the diaphyseal site, and had little or no effect at the wrist site—almost exactly what this more recent Danish study has shown.

Both of these studies thus yield the same conclusion, and the studies are, in fact, consistent, not only with one another, but also with the Yugoslav and a number of other studies as well. We have already noted that the Yugoslav study showed a substantial reduction in hip fracture rate in persons with high calcium intakes, but no difference in wrist fracture rate. In both of these intervention studies, calcium has no significant effect on the metaphyseal bone of the wrist. The effect, rather, is on diaphyseal bone, which many workers believe to be of more importance for the problem of hip fracture (*54*). These studies are also consistent with another observation from the Yugoslav study, namely, that bone loss appeared to occur with age, even in the high calcium region.

It seems likely that, in addition to estrogen withdrawal at menopause, involutional bone loss is produced in part by decreased mechanical loading of the skeleton, and by accumulation of structural errors (such as fenestration of trabecular plates). The National Aeronautics and Space Administration bedrest studies (*55*) showed that high calcium intake cannot suppress the bone loss of immobilization, and would not be expected to have any effect on the bone loss associated with structural errors.

That low calcium intake contributes not only to low bone mass but to fracture was strongly suggested by the recent report of a 14-year prospective study of hip fracture in an aging population (*56*). Of a variety of nutritional, life-style, and environmental variables, calcium intake was the most strongly correlated. Persons with calcium intakes under 470 mg per day had more than three times the number of hip fractures as persons ingesting intakes above 765 mg per day. This finding is congruent with the hip-fracture-protective effect noted in the Yugoslav study (*25*), and is of approximately the same magnitude as the protective effect reported for estrogen prophylaxis.

Estrogen prophylaxis, of course, is not on trial here. Such a large body of convincing evidence exists concerning the protective effects of estrogen on the skeleton that its value cannot be in doubt (*14*). It is not, however, a universally accepted therapy, principally because of many problems, both medical and value-related, which center about its use. Furthermore, it is not a panacea, since any clinician with experience in the management of osteoporosis is familiar with patients who, despite having received estrogen replacement therapy, nevertheless have typical compression fracture disease of the spine. Current estimates from epidemiologic studies suggest that estrogen prophylaxis may reduce the risk of fracture by from 40 to 60 percent (*16*). Such a reduction would be a tremendous accomplishment if it could be achieved across the U.S. population. However, because the reduction is less than 100 percent (and perhaps substantially so), the multifactorial character of involutional bone loss and osteoporosis is underscored.

Thus, the concern about calcium intake should not be cast in adversarial terms, as if it were calcium versus estrogen. Rather, it is calcium and estrogen, and the issue ought to be: What is the optimal calcium intake for middle-aged women? That is, what is the intake that will ensure that calcium deficiency is not contributing to involutional bone loss, thereby adding to the fracture burden of the elderly?

Calcium in Established Osteoporosis

Although this review has been concerned primarily with the relationship between dietary calcium intake and *prevention* of osteoporosis, it is instructive to look at recent treatment studies in which calcium has been used as a component in the therapy of established osteoporosis. This is not, strictly speaking, a pharmacological use of calcium, inasmuch as the intakes involved in the various published studies are all in the range that the foregoing evidence would suggest is simply the requirement of middle-aged and elderly women. Thus, data describing the effect of calcium in osteoporotic women can be used, with some caution, as a surrogate for the study of the effects of calcium in non-osteoporotic women of the same age.

The first such evidence was presented in a composite of several studies from the Mayo Clinic by Riggs and colleagues (*57*). This study indicated that osteoporotic women supplemented only with calcium and vitamin D were able to achieve about a 50 percent reduction in fracture rate, relative to untreated controls, over 1–2 years of observation. These studies were not randomized, and they were mostly performed before modern bone mass measurement technology permitted measurement of spine bone mass. Nevertheless, they support the value of ensuring an adequate calcium intake in elderly women.

Much stronger evidence comes from preliminary results from two large randomized, placebo-controlled trials, one of the calcitriol treatment in osteoporosis (*58*) and the other of fluoride (*59*). Both groups of investigators used calcium supplements (at

intakes in the range of 1,000–2,000 mg per day) for the untreated, placebo-control subjects. The calcitriol study lasted 3 years, and the fluoride study 4 years. One of the most striking features of the available results is that both studies found a complete cessation of bone loss over the entire period of observation in the calcium-supplemented controls.

Conclusions

Involutional bone loss, and the fracture syndromes that we designate osteoporosis, are multifactorial phenomena, with various contributions from inadequate calcium intake, gonadal hormone deficiency, decreased physical activity, alcohol abuse, smoking, qualitative defects in the bony material, the accumulation of structural errors through the many cycles of remodeling throughout life, and probably various as yet poorly recognized environment-related toxicities and nutrient deficiencies. Most of the available evidence indicates that inadequate calcium intake makes an important contribution both to age-related bone loss and to bone fragility, though it clearly is not the only reason for these involutional changes. Abundant evidence indicates that a high peak bone mass, achieved at age 35, is the best single protection against osteoporosis in later life. For that reason, adequate calcium intake is particularly crucial during the period when the skeleton is being formed and consolidated (age 12–35). The aggregate effect of calcium intake in middle-aged and elderly persons, averaged over the entirety of a population, tends to be small, in part because of the difficulties in assessing effective calcium intake, in part because prior calcium intake is of more importance to current bone mass than present intake, in part because the balance between obligatory loss and effective intake is of more importance than intake alone (and obligatory losses are virtually never measured in such studies), but most importantly because virtually all of the studies performed have contained various numbers of both calcium-deficient and calcium-replete individuals. The latter occurs because we have no means of identifying calcium deficiency. By contrast, no study of estrogen effect in the postmenopausal years has ever been carried out in a mixed group of individuals. All such subjects have invariably—and reasonably—been selected precisely because of their estrogen-deficient status.

The 1984 National Institutes of Health Consensus Development Conference (*60*) figures of 1,000 mg per day for estrogen-replete, perimenopausal women, and 1,500 mg per day for estrogen-deprived women, remain the best estimates of what we currently think an adequate calcium intake should be. Such intakes are both safe and natural. While some persons can adapt to intakes substantially below those levels, not all persons can. Since we cannot now recognize those who are calcium-deficient from those who are not, it makes good sense to ensure a generous calcium intake for the entire adult population.

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Panel Session: Nutrition/Exercise

Factors To Consider in the Selection of a Calcium Supplement

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Synopsis

Calcium supplements are widely used, yet many questions remain as to the absorption of various calcium salts. Because the solubility of many calcium salts is dependent upon pH, the type of salt used, the condition of the patient, and the time of administration should be considered. Studies show that many calcium supplements on the market today do not meet standards of quality established in the "U.S. Pharmacopeia" (USP). Consumers must be discerning about the products they purchase. Calcium supplements should be taken with meals to ensure solubility. Calcium carbonate, and particularly tribasic calcium phosphate tablets, are not recommended for patients with achlorhydria. Calcium tablets, like almost all drugs, should be taken with 8 ounces of water or other liquid.

IN SPITE OF the wide use of calcium supplements for the prevention and treatment of osteoporosis, considerable confusion remains about calcium absorption, particularly as to what salt provides optimal bioavailability, and when supplements should be taken. Some of the basic biopharmaceutic and pharmacokinetic principles established for drugs may be applied in considering the administration and absorption of calcium.

For many years, all calcium supplements were thought to be equally effective, as long as an equivalent amount of calcium was ingested. It is increasingly obvious that this is not true. The absorption of calcium is both an active and a passive process. However, regardless of the process involved, calcium must be in solution as ions to be absorbed. Of the various dietary factors that affect absorption, those that have a negative effect (that is, phytates, oxalates, phosphates, and fiber) reduce solubility.

On the other hand, numerous researchers have reported that milk or milk products enhance the absorption of calcium because milk contains a more soluble calcium-protein complex, and milk increases acid secretions and residence time in the stomach; both of these conditions increase the solubility of calcium, and thus promote absorption.

The relative solubility of calcium is complicated by the fact that, for many salts, solubility is dependent on the pH of the dissolution medium. Thus, variations in gastrointestinal pH, which are known to exist, have a direct and substantial influence on dissolution and bioavailability. What does all of this mean when choosing a calcium supplement, and in determining when during the day to take it?

Sources of Calcium for Supplementation

In the past, the choice of a calcium product has often been based on the amount of calcium in a particular chemical compound. Using compounds such