Calcium nutrition and bone health in the elderly

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Adult calcium intake

Calcium intake in the United States has been studied extensively for the past 25 yr. Notable are the Public Health Service Health and Nutrition Examination Surveys (HANES I and II) in 1971 to 1974 and 1976 to 1980 (1-3) and the Food Consumption Surveys (FCS) of the US Department of Agriculture (4). The HANES and USDA FCS data are set forth in Tables 1 and 2 for all age groups from age 10 onward. The intake values of the HANES studies were obtained by 24-h dietary recalls administered by trained dietitians to a representative probability sample of over 28,000 persons from the US population.

In general all three studies show similar patterns. The typical US male consumes from 1.2 to 2.0 times as much calcium as the US female, with the differences being greatest between ages 15 and 50. In general also, Blacks and persons below the poverty level ingest less calcium than do whites and/or those above the poverty level. The differences associated with color or income, however, are on the order of 5 to 20%, and hence are considerably smaller than the differences associated with sex.

Tables 1 and 2 include intake data extending back to before the pubertal growth spurt, despite the fact that the focus herein is nutrition in the elderly. The reasons are that early nutrition may be important in determining peak adult bone mass (see Appendix 1), and that early food habits may be important in determining lifelong consumption patterns. Further, although not conclusively proven, it is likely that peak adult bone mass may have more influence on fracture susceptibility in the elderly than any other single factor recognized to date (5).

Distribution of intakes for each age group is depicted in Figure 1 for the HANES I data. Similar patterns obtain for the HANES II and the FCS data. Males have both higher intakes and a broader range of intakes than do females, with 60 to 70% exhibiting intakes on any given day above the recommended dietary allowance (RDA) for the US from age 18 to 35, and with 75% above at least 500 mg/day for most of their adult lives. By contrast, after age 15 more than half of US women on any given day have calcium intakes below the RDA, and this proportion rises with age. During the years 18 to 30, when peak bone mass is developing, more than two-thirds of all US females ingest less than the RDA on any given day; and after age 35 more than 75% of US women have calcium intakes less than the RDA. Fully one-fourth of all US females of all ages are found to ingest less than 300 mg on any given day.

These observations that substantial fractions of the population have an intake well below the RDA are not new. As early as 1955 the Household Food Consumption Survey of the USDA (6) had noted that calcium was one of three nutrients most often found to be ingested at levels below the RDA.

Effective calcium intake in the elderly

Effective calcium intake is a complex product not only of dietary content, but of absorp-
TABLE 1
Median calcium intake (mg) in the US by age (all persons)

<table>
<thead>
<tr>
<th>Age</th>
<th>10-14*</th>
<th>15-19*</th>
<th>20-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1971-74</td>
<td>1170</td>
<td>1195</td>
<td>888</td>
<td>867</td>
<td>737</td>
<td>688</td>
<td>680</td>
</tr>
<tr>
<td></td>
<td>HANES II</td>
<td>1035</td>
<td>1142</td>
<td>1001</td>
<td>805</td>
<td>716</td>
<td>733</td>
<td>685</td>
</tr>
<tr>
<td>Women</td>
<td>1971-74</td>
<td>895</td>
<td>672</td>
<td>570</td>
<td>547</td>
<td>487</td>
<td>491</td>
<td>478</td>
</tr>
<tr>
<td></td>
<td>HANES II</td>
<td>810</td>
<td>608</td>
<td>565</td>
<td>535</td>
<td>509</td>
<td>474</td>
<td>475</td>
</tr>
</tbody>
</table>

TABLE 2
Mean* calcium intake (mg), by age (USDA food consumption survey, 1977 to 1978)

<table>
<thead>
<tr>
<th>Age</th>
<th>12-14</th>
<th>15-18</th>
<th>19-22</th>
<th>23-34</th>
<th>35-50</th>
<th>51-64</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1077</td>
<td>1194</td>
<td>983</td>
<td>830</td>
<td>764</td>
<td>702</td>
<td>714</td>
</tr>
<tr>
<td>Women</td>
<td>864</td>
<td>774</td>
<td>630</td>
<td>604</td>
<td>515</td>
<td>532</td>
<td>575</td>
</tr>
</tbody>
</table>

* The USDA data are readily available only as means, whereas both mean and median data are available for HANES. The FCS means are somewhat lower than the corresponding HANES means.

FIG. 1. Median calcium intakes for US males and females ages 18 to 70, derived from HANES I data (1). Ranges about median values represent the 25th to the 75th percentiles.

Calcium absorption and age

The two determinants of effective calcium absorption are the amount of calcium in the diet and the efficiency of its absorption. Calcium is absorbed by both active and passive transport systems. The active transport is concentrated in the upper small intestine, is mediated by 1,25(OH)₂ vitamin D (calcitriol), and is saturable.

Intestinal calcium absorptive efficiency decreases after middle age, whether measured by metabolic balance techniques, radioactive calcium tracer techniques, or directly by intestinal intubation methods (7-12), but the pattern of change detected depends on the measurement technique used. Using metabolic balance studies, absorption appears to show a linear decline from age 40–50 yr. Double isotope studies (100 mg calcium carrier) show a linear decrease in absorption from age 30 yr. Single isotope studies using a small (20 mg) calcium carrier show no change in calcium absorption before age 65 yr, and then a gradual fall. Presumably, if the decrease in absorption is seen with even a small carrier load, this must indicate a decrease in both the active transport system and the diffusion system in the upper small intestine.

The use of a triple lumen perfusion technique to study active transport has shown that elderly subjects appear to have decreased absorption of calcium compared to normal
subjects. They also show an impaired response when placed on a low calcium diet (12). Malabsorption of calcium was not shown in calcium balance studies performed in elderly people by Bogdonoff et al (13).

Under normal circumstances the efficiency of intestinal calcium absorption is carefully regulated to meet the body's needs for calcium (14). Thus, efficiency of calcium absorption normally increases when dietary calcium is low, and decreases when dietary calcium is high. This adaptive response plays a major role in maintaining calcium homeostasis despite marked variations in dietary calcium (14, 15). In elderly individuals, however, this adaptive response is blunted, and the efficiency of intestinal calcium absorption increases relatively little when dietary calcium is restricted (12). The major controlled variable regulating the efficiency of intestinal calcium absorption is calcitriol, the hormonal form of vitamin D (16). Serum levels of calcitriol are reported to be lower in elderly subjects than in young adults (7, 17, 18), but not all investigators have confirmed this finding.

Intestinal calcium absorption has been found to be reduced more in elderly people with osteoporotic fractures than in subjects of the same age without osteoporosis (7, 19–22), and patients with osteoporosis are also reported to have lower serum levels of calcitriol than age-matched controls (7). Despite some decrease in intrinsic absorptive capacity, this factor is probably not limiting, inasmuch as response to amounts of calcitriol in the physiological range can readily be demonstrated in osteoporotics in whom calcitriol levels may be low (7, 23). Riggs et al (24) have described a subset of osteoporotics who exhibited poor absorption, high iPTH levels, and inappropriately low values for calcitriol (23). Hence impairment of conversion of calcidiol to the active hormonal form of the vitamin appears to be an important component of the decreased absorption efficiency found in some subjects. All investigators agree, however, that serum levels of calcitriol in young adults and in elderly or elderly osteoporotic adults overlap to a significant degree.

Comment

It is well established that calcium absorption efficiency declines with age, and it seems likely that some of this change is due to a fall in circulating calcitriol levels. This fall is subject to at least two different interpretations, with differing significance for calcium and vitamin D nutrition. Under one hypothesis, deficient renal secretion of calcitriol, brought on by age-related decreases in renal function, deficiencies of gonadal steroids, or other factors, is primary. Malabsorption of calcium follows and the reduced flow of calcium into the blood stimulates a reactive increase in parathyroid hormone (PTH) secretion, which in turn increases renal secretion of calcitriol. (See “Vitamin D and bone health in the elderly, p 1014). While this response may maintain serum levels of calcitriol, the elevated levels of PTH produce bone resorption and eventual osteoporosis. Under this hypothesis, age-related bone loss occurs as a form of mild calcitriol deficiency with mild compensatory parathyroid-mediated bone loss.

Under another hypothesis the primary abnormality is an imbalance between bone resorption and bone formation, brought on either by reduced physical activity, age, estrogen deficiency, or other factors. Because calcium released from the skeleton exceeds calcium taken up by the skeleton, PTH secretion is suppressed, with consequent reduction of calcitriol synthesis. Reduced efficiency of intestinal calcium absorption would thus constitute an appropriate adaptation to net flux of calcium from bone, exactly analogous to the adaptations which take place in response to the resorptive excess of bed rest. Both hypotheses have in common reduced efficiency of intestinal calcium absorption, reduced levels of calcitriol in the serum, net bone resorption, and osteoporosis. However, the causal sequences are directly opposite, and the PTH levels differ under the two hypotheses.

In discussing the complicated and often discrepant evidence for and against these hypotheses, it is important to bear in mind that both may be correct, but in different individuals. Osteoporosis is currently defined by exclusion as a clinical syndrome, without specific pathophysiological characteristics. It is thus possible that in different individuals with osteoporosis either hypothesis may be correct; and it becomes a matter of determining the relative frequency of each type.
Radioimmunoassays for the measurement of PTH in serum indicate that secretion of this hormone is elevated above normal in approximately 15% of patients with osteoporosis (25-29). At least two groups have reported a syndrome of osteoporosis with increased serum iPTH and inappropriately low serum calcitriol, consistent with the first hypothesis (24, 30). However, these same investigators (7, 26, 27), as well as others, have reported that in most patients with osteoporosis, PTH levels measured by radioimmunoassay are normal (31, 32) or low (33) for the person's age, and the latter finding is consistent with the second hypothesis. Interpretation of these data is made difficult by the fact that assayable iPTH levels in serum increase with age (27, 29, 34, 35). Thus a PTH level in an elderly individual can be considered normal if contrasted with other individuals of the same age, or elevated if contrasted with younger individuals. This problem is further complicated by the well-known difficulties of measuring small but biologically significant variations in PTH secretion using presently available radioimmunoassays of the peptide in serum (36).

An alternative approach to this problem involves the administration of exogenous PTH to stimulate renal secretion of calcitriol. This approach circumvents the conceptual and technical difficulties that surround the interpretation of serum parathyroid hormone levels. By infusing exogenous PTH, the feedback loop regulating calcitriol synthesis can be opened, greatly simplifying interpretation of the resultant data.

When synthetic human PTH fragment 1-34 (hPTH 1-34) is infused intravenously for 24 h, serum levels of calcitriol increase significantly in healthy, young individuals, but in one report increased little, if at all, in elderly osteoporotic subjects (37). Such results suggest failure of the renal 1-α-hydroxylation system. However, the identical stimulation test does increase serum calcitriol levels normally in some elderly individuals with osteoporosis, arguing again for the presence of pathophysiological heterogeneity in the population of patients currently classified on clinical criteria as having "osteoporosis." Furthermore, other investigators (using a stimulation test which involves the subcutaneous administration of large doses of PTH) find that the ability to augment serum calcitriol levels is identical in osteoporotic individuals and in age-matched controls (38). Whether these discrepant results reflect differences in the control populations used (healthy, young normals versus age-matched elderly individuals without fractures), differences in the doses of PTH administered (physiological versus pharmacological), or differences in the osteoporotic populations samples, is at present unclear.

Under either hypothesis the administration of exogenous calcitriol would increase the efficiency of intestinal calcium absorption, increase the total amount of calcium absorbed (if dietary calcium remained constant), and decrease PTH secretion (7, 39-43). However, under the first hypothesis one would anticipate that the absorbed calcium would largely be retained in the skeleton (at least initially), whereas under the second hypothesis, the absorbed calcium would be excreted in the urine. The actual results of experiments involving the administration of calcitriol or 1-α-hydroxy D₃ to elderly individuals with idiopathic osteoporosis are divergent. When calcium balance has been carefully measured both before and during the administration of calcitriol, both kinds of results have been reported (23, 41, 45-47). In one 2-yr study of calcitriol administration an increase in skeletal mass of osteoporotic individuals was found on bone biopsy, accompanied by a significant reduction in fracture frequency (23).

It would be extremely desirable to evaluate in the same individuals the serum levels of calcitriol and PTH, the effects of exogenous PTH administration on calcitriol secretion, and the effects of exogenous calcitriol on calcium balance and skeletal mass. Until such correlated studies are carried out, it will remain difficult to establish the pathophysiological significance and the therapeutic implications of these intriguing new insights into the interrelationships of calcium nutrition, calcium homeostasis, and aging.

Nutrient-nutrient interactions

Phosphorus. Phosphorus intake has long been held to influence bone growth and calcium balance, with excess phosphorus (or a low Ca/P ratio) being associated with various skeletal defects. Draper and Bell (48) have
recently reviewed the subject in detail. Almost all of the evidence of harmful skeletal effect, however, is in rapidly growing animals. There is very little direct evidence in man to suggest that even broad variations in phosphorus intake or in dietary Ca/P ratio have any influence on net calcium utilization or on bone balance, and indeed some evidence to the contrary.

What seems reasonably well established is that diet phosphorus and urine calcium are inversely correlated, even within the range of usual dietary phosphorus intakes (49, 50), and that, when phosphorus intake is increased, plasma calcium falls slightly, plasma phosphorus rises, plasma iPTH levels rise, and resorption surface on bone biopsy increases. Deterioration of calcium balance or bone loss has not, however, been observed in human studies. Nevertheless these observations have been interpreted to suggest that the mild phosphatemia associated with increased intake binds circulating calcium, which leads to increased release of PTH and consequent increase in bone resorptive activity, which in turn is presumed to be an undesirable or deleterious phenomenon. The same data are, however, susceptible of a quite different and, it seems to us, more plausible interpretation.

The quite small hyperphosphatemia produced by increased phosphorus intake within the usual dietary range does not result in appreciable calcium binding. This is not surprising, given the fact that plasma and extracellular fluid are only roughly half-saturated with respect to the calcium phosphate form most likely to precipitate at physiological pH (50a). Further, the slight but sustained depression in plasma calcium, despite increased PTH release, would require continuing loss or sequestration of the putative calcium-phosphate complexes, and this simply is not observed. A better explanation for the slight hypocalcemia and the increased PTH release is found in the pronounced depressive effect of phosphate on PTH stimulation of osteoclasts, first noted by Raisz (51) in organ culture. This resorptive antagonism explains also the increase in resorption surface noted on biopsy.

The data supporting the second interpretation can be briefly summarized as follows. In humans calcium balance does not deteriorate when dietary phosphorus is increased by a factor of more than three (49, 50, 52). In the study of Goldsmith et al (52) calcium balance actually improved slightly during phosphate therapy of osteoporosis (despite increased iPTH and resorption surface). Nor does calcium phosphate precipitate in soft tissues in detectable quantities, even in persons receiving long-term, high dose phosphate therapy for renolithiasis.

Spencer et al (50), studied calcium balance at 0.8 and 2.0 g P/day. No change in balance occurred as a result of changing phosphorus intake at low, normal, or high calcium intake levels. Finally, Heaney and Recker (49) have reported effects of variations in phosphorus intake in 179 normal perimenopausal women. They found that, as expected, urine calcium falls as phosphorus intake rises, but that intestinal calcium secretion rises at a rate slightly greater than the fall in urine calcium. (This change in intestinal calcium secretion cannot be the result of binding of calcium by phosphorus in the lumen, since the effect is on the entry into the intestine.) Hence, while variations in phosphorus intake have clear effects on calcium handling, and probably on bone remodeling as well, these effectively cancel one another, and thus balance is not appreciably influenced.

**Protein.** Much work has been done on the effects of protein on calcium balance, extending back more than 50 yr (53). When intake of dietary protein, as an isolated nutrient, is increased, urine calcium increases proportionately (53–58). But no change in calcium absorption or in endogenous fecal excretion occurs (49, 59). Hence the increase in calciuria translates directly into a negative balance shift. The effect is produced by a combination of an increase in the glomerular filtration rate and a decrease in tubular calcium reabsorption, without a change in plasma calcium (60, 61). The slope of the fractional increase in urine calcium on dietary protein, in the three groups of studies cited above, ranges from +0.48 to +0.52, which means simply that a doubling of protein intake results in an approximate 50% increase in urine calcium. (For comparative purposes it is worth noting that this calciuric effect of doubling protein intake is greater than that produced by doubling of diet calcium.)

Because protein intake does not change as
an isolated nutrient, but in concert with other constituents of natural protein sources (e.g., phosphorus), other nutrient-nutrient interactions mask the full hypercalciuric effect of protein. The available literature is divided as to whether increased intake of natural protein products produces any significant negative balance shift. Spencer, et al (59), in nine patients, have reported that it does not, whereas Cummings et al (62) found the opposite. Marsh et al (63), working with vegetarian and omnivorous women reported more rapid postmenopausal loss among the omnivorous women, but protein intakes in that study are not given, and it is not certain whether protein source or protein amount was the factor responsible for the difference. Canadian and Alaskan eskimos subsisting on a high meat diet, have been found to lose bone more rapidly with age than do US whites (64), but other dietary differences which protein or protein amount was the factor responsible for the difference. Hence, while more work clearly needs to be done, there appears to be sufficient evidence to allow the conclusion that protein intake in excess of need results in effectively reduced retention of absorbed calcium, and hence a relative increase in calcium intake requirement.

Fiber. There is increasing interest in the effect on calcium metabolism of high fiber diets, in view of their potential use for control of serum lipids or of glucose absorption in diabetic subjects. Enormously high intakes of dietary fiber do seem to carry dangers of excessive losses of trace minerals in the large stools produced. With regard to their effect on minerals, it is thought that natural fibers have a chelating effect on calcium. McCance and Widdowson (65) showed in 1942 that the absorption of calcium, magnesium, and phosphorus declined when white flour was replaced by flour of lower extraction rates and that individuals developed negative calcium balance when whole meal wheat bread constituted a high proportion of the diet. Calcium balance studies carried out in patients on a low fiber diet developed increased fecal excretion of calcium and zinc when 10 g of cellulose were added to the diet (66). Also, if cellulose was added to a high fiber diet, fecal excretion of calcium still increased. The same group studied 20-day balances on high fiber consumption in the form of bread made partly from wheaten whole meal. There was an increased fecal excretion of calcium in the patients studied. This was in contrast to the findings on white bread. These findings were of local importance in Iran where the Bazari bread, although containing more calcium than white bread, was nutritionally inferior because of its high fiber and high phytate content (67). (Bread supplies 50% of calorie needs in children in Iran.)

Other studies have shown that unrefined cereal products can interfere with absorption of calcium and zinc (68). More recent studies by Cummings et al (62) showed that the addition of 31 g of dietary fiber (from wheat) significantly increased fecal weight, shortened intestinal transit time, and increased fecal bile acid excretion. Some subjects studied on a high protein diet developed more negative calcium balance when fiber was added. In the studies by Kelsay et al (69) 12 men were studied on control diets containing fruit and vegetables (high fiber diet) or fruit and vegetable juice (low fiber diet) for a period of 26 days. Calcium balance on the low fiber diet was +72 mg/day and changed to -122 mg/day on the high fiber diet. Sandstead et al (70) have also shown that added fiber makes calcium balance more negative. They calculate that an increase in fiber intake of 26 g increases calcium requirement by 150 mg/day.

There is sufficient evidence to indicate that reasonable amounts of fiber appear to affect calcium balance in short-term studies. Whether this becomes a factor in the long-term use of fiber remains yet to be answered. It is unlikely at the present time that the fiber
content in most Western diets approaches the levels used in these studies, but fiber could be a risk factor in certain individuals.

Drug-nutrient interactions

Diuretics. A recent study by Christiansen (71) showed that thiazide diuretics prevented bone loss in normal postmenopausal women for 6 months, after which the women lost bone at the same rate as those on placebo. Preliminary information by Christiansen (Gallagher JC, personal communication) is that plasma calcitriol levels fall on thiazides. The resulting decrease in calcium absorption may account for the long-termescape on thiazides.

Alcohol. There are a number of reports describing association between alcoholism and osteoporosis. However, the data reported are not always in agreement. Saville (72) reported a decreased bone mineral content on iliac crest biopsy in young deceased alcoholics. Nilsson and Westlin (73), found a significantly decreased bone mass in the femurs of alcoholics, but on subdividing the cases they found that a low bone mass only occurred in those patients who had undergone partial gastrectomy. In a further study, Nilsson measured radial densitometry in three groups: 56 men with a history of alcoholism, 58 men admitted to a hospital department for alcoholics, and 35 men with a history of severe alcoholism who were patients in an orthopedic department. The reduction of bone mass with age was significantly greater in alcoholics. This decreased bone mass amounted to about a 25% reduction compared to the normal mean at age 70. At a younger age, there was no difference in bone mineral content between controls and alcoholics. Decreased bone mass in alcoholics has also been reported by Darlin and Lamke (74). In contrast, Roginsky et al (75) showed a normal skeletal mass in alcoholics with or without cirrhosis. Their results were based on measurements of total body calcium by neutron activation analysis and also radial densitometry.

Possibly the reported differences can be explained by variations in vitamin D nutritional status between northern European countries and USA. Lund et al (76) divided alcoholics into three groups, fatty liver disease only, compensated cirrhosis, and decompensated cirrhosis. Serum calcidiol levels were lower in all groups compared to normals, even in summertime when normal subjects showed a seasonal rise. After the administration of 1200 units of vitamin D, significant increases in serum calcidiol occurred after 7 days suggesting that absorption of vitamin D was normal even in advanced liver disease. The fact that the patients responded to very small doses of cholecalciferol suggests that deficient intake was the primary cause of low calcidiol levels. Exposure to sunlight was not quantitated in this study. In one study from Scandinavia, an increased incidence of alcoholism has been reported in patients with hip fractures by Nilsson (77).

Antacids. There is little information published on the use of antacids in the elderly. In a study of 1500 people in a small community, 8% took gastrointestinal drugs that were either laxatives or antacids (78); of these, 4% had doctors' prescriptions and 4% bought over-the-counter drugs. Antacids are normally available as aluminum hydroxide, magnesium hydroxide, simethicone, calcium carbonate, or various combinations of these, the most common combinations being aluminum and magnesium hydroxides. (Calcium carbonate is treated elsewhere in this paper.) The adverse effects of aluminum-containing antacids on mineral metabolism have been reviewed recently by Spencer and Lender (79). They include hypercalcuria, bone resorption, impairment of fluoride absorption, and phosphorus depletion, all of which may contribute to bone disease in the elderly.

Lactase deficiency

Intestinal lactase deficiency has attracted some attention in recent years because of its possible association with osteoporosis, either through impaired calcium absorption or through reduced intake of milk secondary to intolerance (80). In small animals lactose improves absorption of calcium. In studies of humans with normal lactase, some groups have shown that lactose enhances calcium absorption (81, 82). But in lactase deficiency, two groups (81, 82) reported that lactose inhibited calcium absorption and one group reported the opposite (83).
Lactase is universally present in normal infants and then gradually declines during the early years. Lactase deficiency is extremely common among Black and Asian adults and variably present among adults living, or having their family origins in, northern and western Europe (84). The associated symptoms may be severe enough to put many off drinking milk altogether. Nevertheless both Black and Asian adults have learned that they can tolerate milk if taken in moderate quantities at one time (85, 86). Individuals sensitive to small quantities of lactose can continue to eat calcium-rich foods by selecting cheese, cultured milk products, and lactose-reduced milk, or by taking smaller, more frequent servings of milk.

Birge et al (80) found nine of 19 osteoporotic patients to have lactase deficiency; whereas none of the 13 control subjects were deficient. Newcomer et al (87) compared 30 women with osteoporosis to 31 female control subjects. Eight of the osteoporotics had lactase deficiency as contrasted with only one of the control subjects (p < 0.05). None of the lactase deficient subjects had symptoms. Kocian et al (88) studied cortical thickness of the clavicle in patients after partial gastrectomy and found significant thinning only in the subjects with lactase deficiency. In Newcomer's study, the lactase-deficient subjects, although not overtly milk intolerant, did consume significantly less calcium than the normal lactase group (530 mg daily versus 811 mg daily).

Menopausal effect on calcium requirement

The onset of rapid bone loss in women is closely associated with menopause. By definition, therefore, a distinct negative balance shift occurs at the time of menopause. The relationship of this shift to dietary calcium intake has been a matter of controversy for many years. Heaney et al (89) in 274 studies in 168 normal perimenopausal women has shown that calcium balance is a function of calcium intake, both before and after menopause, but that the parameters of the relationship are different in the presence and absence of estrogen. After menopause, for any given intake, absorption is about 14 mg less, and for any given absorbed load, urine calcium is about 17 mg greater than before estrogen withdrawal. Thus both absorption and retention deteriorate after menopause, with a net balance change of −0.025 g/day. Estrogen treatment of postmenopausal women abolishes these differences.

These decreases in availability and utilization of dietary calcium after menopause appear to contribute to the rapid postmenopausal acceleration of age-related bone loss. From the fact that intake and balance remain correlated in the absence of estrogen, it can be inferred that the balance deterioration can be offset either by estrogen replacement or by increased calcium intake. Equivalently, therefore, estrogen withdrawal produces an increase in the calcium intake requirement. The slope of the relationship between intake and balance is such that an increase in calcium intake of nearly 500 mg/day is required to produce the same balance effect as moderate doses of estrogen.

Illness, immobilization, and exercise

Bone mass decreases whenever physical activity is reduced. This is seen most clearly in studies of immobilized human subjects (90, 91). Available evidence suggests that loss begins immediately or at least very soon after onset of immobilization. On full bedrest, the daily calcium loss is on the order of 200 to 300 mg. The loss has two components: increased urinary loss and decreased absorption from the diet. Increased calcium intake alone does not appreciably alter the basic pattern of loss, but when given with extra phosphate slows loss somewhat (92, 93). Recovery of lost mineral by the adult skeleton has been demonstrated in immobilized subjects who resumed normal physical activity (94). While the bone loss of disuse is not nutritionally related, nevertheless if recovery is to occur after remobilization, the diet must contain sufficient calcium to allow storage in amounts sufficient to offset prior loss.

Available human data on the effects of immobilization are essentially limited to astronauts, patients with paralytic disease, and normal volunteers on bedrest, (90, 91, 95, 96). Few data are available on the effects of medical or surgical illness associated with periods of bed rest and reduced physical activity. However, it seems safe to conclude that all such situations are associated with negative
calcium balance, unrelated to dietary intake. Such negative balance would be due at least to the decreased physical activity of illness and possibly also to its general catabolic effects. In any case illness creates a skeletal deficit that can in many, and perhaps most, cases be repaired after recovery from the primary disorder, so long as nutritional sources permitted.

Aloia (97) and Whedon (98) have recently reviewed the effects of exercise on bone mass. The evidence indicates that exercise increases bone mass both during recovery from immobilization, and as in athletes. In states of declining bone mass, exercise acts principally to slow the rate of loss, although even in elderly and osteoporotic individuals actual increases in mass have been reported with exercise regimens (97, 99). Such exercise-related increases in bone mass mean positive calcium balance and hence more effective utilization of dietary intake. Intake often changes with illness and immobility, as well as with exercise. However, this is not a satisfactory explanation for change in balance, since calcium absorption efficiency has been observed to be decreased in immobilization (99a); and calcium supplements alone are not effective in preventing the calcium loss of immobilization (93).

Without attempting to describe the complex mechanisms involved, it can be simply stated that decreased physical activity leads to decreased efficiency of utilization of ingested calcium, and increased activity, to improved efficiency. Finally as noted elsewhere, a diet just adequate to permit calcium balance in a healthy adult may not provide for the positive balance required to offset prior illness-related losses.

Dietary requirement for calcium in the elderly

RDA

An “allowance,” as distinguished from a “requirement,” is an intake sufficient to meet the needs of almost all healthy persons, ie, it takes account of interindividual variation in need, and is set at a level such that it is above the probable requirement of 90 to 95% of the population. The RDA for calcium in the United States is 800 mg/day for nonpregnant, nonlactating adults (100); in the United Kingdom, 500 mg (101); the WHO standard is 400 to 500 mg. By implication these values are intended to apply to all adults of both sexes.

These national differences in values for the RDA highlight the central problem with which this paper deals. If osteoporosis is in any significant sense caused or aggravated by calcium deficiency, then by definition the intake of most adults in developed countries is too low, simply because such a significant fraction of all such adults develop osteoporosis. On the other hand, if calcium intake plays no important role in osteoporosis as it occurs in contemporary society, then the calcium intake of most persons in developed countries is adequate and the current RDA in the US is certainly higher than necessary. Once again it is a matter of definition: if the population is healthy on an intake substantially below the RDA (vide supra), then the RDA is higher than necessary.

Determination of requirement

Irwin and Kienholz (102) in 1973 assembled over 500 published studies relating to human calcium requirement. Their review illustrates well three basic approaches used to estimate calcium requirements: 1) epidemiological methods, used to evaluate the health of the population as a function of calcium intake; 2) “factorial” methods, which calculate intake requirements on the basis of matching obligatory losses; and 3) balance studies in normal persons on varying intakes.

Epidemiological methods. As noted, the epidemiological approach is beset by the problem of circularity: we cannot estimate health relative to calcium until we can decide whether human osteoporosis is a calcium-related health problem. Logically we ought to be able to break out of this circle by looking for effects of self-selected differences in calcium intake on bone mass or an osteoporotic fracture frequency, or conversely by looking for differences in calcium intake between osteoporotics and age-matched controls. Evidence in these regards is decidedly mixed. We will examine this evidence under four headings: 1) customary calcium intake and bone mass; 2) calcium intake and rate of age-related bone loss; 3) calcium intake and os-
teoporotic fracture; and 4) calcium intake in osteoporotics.

Relation of Customary Calcium Intakes to Bone Mass. Garn et al (103), in several careful studies, have been unable to find any appreciable relationship between current calcium intake and current bone mass, either in elderly subjects or in persons across a broad range of ages. Similarly, Smith and Rizek (104) found no significant relationship between current intake and current bone mass. Smith and Frame (105) found no relationship between femoral cortical thickness, metacarpal cortical thickness, or vertebral density (graded visually) with calcium intake in a study of 220 women in whom calcium intakes ranged from 150 to 2100 mg/day. Hurxthal and Vose (106) measured bone density in the lumbar vertebra by a radiodensitometric technique in 404 subjects. Lifetime calcium intakes were calculated by diet history. There was a weak but significant correlation of bone density with calcium intake.

More recently, analysis of the relationship of calcium intake to metacarpal cortical area and percent cortical area was performed on the data collected in the Ten-State Nutrition Survey of the United States (107). A weak but significant correlation of calcium intake with bone mass was found.

A study from Switzerland reported in abstract (108) found no differences in bone mass between 3000 subjects in Geneva and 1200 subjects in two mountain villages, although calcium intakes were different (for males 1100 mg/day in Geneva and 2150 mg/day in the villages, for females 870 mg/day in Geneva and 1270 mg/day in the villages). The methods used for determining calcium intake are not given. By contrast Matkovic et al (109) found clear differences in bone mass in two Yugoslav communities distinguished principally by an approximate 2-fold difference in calcium intake. Bone mass was higher at all ages in both men and women in the high calcium district. Apparent rate of loss with age was the same in both districts for both men and women, and the principal reason for the mass difference appeared to be the fact that persons in the high-calcium district started with a higher bone mass at their adult peak than did persons in the low-calcium district. (Fig 2 illustrates this phenomenon for men in the two districts.)

Calcium Intake and Rate of Age-Related Bone Loss. Studies of cortical bone loss using radiogrammetry on the second metacarpal have been performed by Garn et al (110) in over 5800 subjects from seven countries. (See Appendix 3, “Bone mass measurement.”) The rate of loss was approximately the same in all groups, despite wide variations in calcium intake, ranging from 300 to 500 mg/day in those with low intake, to 900 to 1500 mg/day in those with high intake. Some ethnic groups ingesting low levels of calcium had higher skeletal mass than others on lifelong high intakes (103).

Calcium Intake and Osteoporotic Fractures. Cave and Nordin (111) in a study of international patterns of bone loss, using spine films to judge the prevalence of osteoporosis, noted an inverse rank-order relation between osteoporotic fracture frequency and calcium intake. Japan, with the lowest calcium intake, had the highest prevalence of osteoporosis, and Finland, with the highest calcium intake, the lowest prevalence. However, Gambia and Jamaica, with relatively low calcium intakes, had a low prevalence of osteoporosis. Interpretation of these results is complicated by ethnic diversity and by unavoidable imprecision in method.

The study of Matkovic et al (109), previously cited, contained data on fracture rates as well as bone mass. Femur fracture rates...
were substantially lower at all ages in both men and women from the high calcium district; however, no differences were noted in proximal forearm fracture frequency. Such studies raise the possibility that the relationship between calcium intake and bone health, other things being equal, needs to be sought, not at the time when osteoporosis develops, but 30 to 40 yr earlier, when skeletal massiveness is determined.

**Calcium Intake in Osteoporotics.** Table 3 summarizes data from the several studies which have compared calcium intakes of patients with clinical osteoporosis to controls. Methods of estimating calcium intake vary widely among these studies. Further, control subject intakes in the US studies are quite different from the HANES data (1, 3). Nevertheless virtually all studies produce the same conclusion: osteoporotics, other things being equal, give histories of lower calcium intakes than nonosteoerotic controls.

**Comment.** Much of the epidemiological evidence is based on various measures of bone mass and on calculations of calcium intake in individuals and for populations. It is assumed that the measurements made reflect changes in the skeleton as a whole, and that all parts of the skeleton change in time correspondingly. These assumptions may not be entirely valid. (See Appendix 3.) These studies are also dependent on an adequate evaluation of calcium intake of individuals or of a population. In many cases, sufficient information is not provided to judge the adequacy of dietary intake estimates. This problem is discussed by Garn (103). Estimates drawn for small groups of individuals, especially when judging long-term calcium intake by a questionnaire, are probably not very accurate. Real calcium intake in nonindustrialized nations is often underestimated by omitting nonfood sources of calcium (eg, lime or clay chewed with coca or betel leaves, calcium-containing clays mixed with cereal gruels, etc) (116).

In most of the published epidemiological studies of calcium intake, only weak, or in many cases no correlation, has been found between dietary calcium and bone mass, assessed either by rates of bone loss or by cross-sectional studies. However, other factors that affect skeletal size and rates of loss, eg, genetic predisposition, physical exertion, adaptation to low calcium intake, and other types of nutrients, may mask any effect due to the differences in calcium intake alone.

A fairly large number of published reports suggest that patients with clinical osteoporosis have a lower calcium intake than controls. These studies are subject to the problems of accurate evaluation of dietary calcium intake, especially when conclusions for lifetime dietary habits are based on short interviews; however, there is little reason to believe that such difficulties would systematically underestimate intake in osteoporotics relative to normal subjects. Furthermore there is considerable disparity in dietary calcium in the various groups studied, such that controls in some groups had lower intakes than osteoporotics in other studies.

Nevertheless most authors are agreed that osteoporotics ingest less calcium than normal control subjects. The studies differ widely in quality, method, and rigor, but not in conclusions. Further, in the two published studies in which fracture has been evaluated, low calcium intakes have been associated with distinctly increased prevalences of hip and spine fractures.

**Factorial methods.** Factorial methods have

### TABLE 3
Calcium intake in osteoporotics

<table>
<thead>
<tr>
<th>Reference</th>
<th>Osteoporotics</th>
<th>Controls</th>
<th>p &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mg/day</td>
<td>mg/kg/day</td>
</tr>
<tr>
<td>Nordin (112)</td>
<td>71</td>
<td>13.4 ± 1.5</td>
<td>9.9 ± 1.1</td>
</tr>
<tr>
<td>Nordin et al (113)</td>
<td>21</td>
<td>807 ± 20</td>
<td>14</td>
</tr>
<tr>
<td>Riggs et al (114)</td>
<td>34</td>
<td>732 ± 64</td>
<td>17</td>
</tr>
<tr>
<td>Hurxthal and Vose (106)</td>
<td>132</td>
<td>617 ± 30</td>
<td>66</td>
</tr>
<tr>
<td>Lutwak and Whedon (115)</td>
<td>53</td>
<td>280</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>385 ± 50</td>
<td>850</td>
</tr>
</tbody>
</table>
been used to estimate average endogenous loss through urine, feces, and skin, and then, by making reasonable assumptions about fractional absorption, to calculate intake levels required to offset such endogenous loss. The weakness with this approach is that endogenous loss through urine and feces is not a constant, but is itself a function of intake, just as is fractional absorption from the diet (see Appendix 2). For a median calcium intake of 500 mg/day (typical for perimenopausal women in the HANES studies), urine calcium averages 143 mg, endogenous fecal calcium 86 mg, and dermal losses 15 to 20 mg, for a total loss of 244 to 249 mg (49). Because both urine and endogenous fecal calcium vary directly with intake there is no "average" value for these losses that has meaning apart from specific intakes. Thus the factorial approach to determining calcium requirement is not able definitively to resolve the difficulty.

Balance methods. The balance approach can take several forms: 1) measurement of balance response to manipulated intake; 2) measurement of the effect of calcium supplements on changes in bone mass; and 3) the observation of balance performance on customary, home intakes. For reasons discussed below the last approach is not equivalent to the first two.

Manipulated Intakes. Nordin (117) summarized published studies of response to manipulated intake levels, noting that the line relating published balances to intakes crossed the identity line at 8.4 mg/kg/day, or 500 to 600 mg of calcium per day. This value, thus, represents a mean calcium requirement. As noted earlier, the recommended allowance for the population would have to be expanded to include 95% confidence limits for that calcium requirement figure. Since the SD is large, a value of 500 to 600 mg for the mean results in a recommended allowance nearer 800 to 1000 mg/day in young adults.

The data in Table 4 include the studies of mean requirement summarized by Nordin, plus other publications of studies in elderly persons. As can be seen, estimated mean requirements range from 200 to 1700 mg/day. There is not sufficient space to discuss adequately the problems involved in interpreting these disparate results, but five factors important to an interpretation of such studies need to be cited.

1) Many of these studies, particularly those yielding values at the lower end of the scale, were performed in young, healthy individuals, many of them males. Such results have uncertain relevance to the elderly, and particularly to the female elderly. Note that the estimated mean intake requirements for subjects specifically designated as elderly range from 830 to 1700 mg and that none of these mean values is as low as the RDA. The weighted mean of the estimates in these studies in the elderly is 1040 mg/day (equivalent to an allowance of roughly 1500 mg/day).

2) Studies obtained in volunteers in non-industrialized nations may be flawed by omission of nondietary sources of calcium, as already noted (116).

3) While certain of these studies showed that some subjects were able to come into equilibrium at low intakes, often the same studies (eg, Reference 14) showed that many individuals were never able to adapt (for as long as 1.5 yr of observation).

4) Generalization to an intake requirement from studies of adaptation ignores the known negative calcium balance consequences of immobilization, of even mild illness, of alcoholic bouts (vide supra), and of the many other indispositions and metabolic vicissitudes that customarily beset adult humans. An intake just adequate for equilibrium during health allows for no compensatory recovery of calcium lost during illness or inactivity.

5) Calculation of requirement from maintenance of balance assumes the adequacy of current calcium (skeletal) reserves. An intake sufficient to maintain equilibrium is manifestly insufficient to allow increase in skeletal mass. This point is important in connection with development of optimal adult bone mass values. Since approximately 10 to 15% of total skeletal mass is normally added between ages 20 and 35, zero balance in subjects in this age range cannot be taken as a criterion of good health or adequate nutrition.

Effects of Calcium Supplements on Bone Mass. The effects of calcium supplementation on various indices of change in bone mass have been reported by several groups. (See Appendix 3, "Bone mass measurement".) Both Recker et al (130) and Horsman et al
TABLE 4
Balance-based estimates of calcium requirements of adults

<table>
<thead>
<tr>
<th>Source</th>
<th>Origin</th>
<th>Subjects</th>
<th>Mean requirement (mg/day)</th>
<th>Mean requirement (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitchell and Curzon (118)</td>
<td>USA</td>
<td>107 men</td>
<td>9.75</td>
<td></td>
</tr>
<tr>
<td>Steggerda and Mitchell (119)</td>
<td>USA</td>
<td>19 young men</td>
<td>644</td>
<td>9.2</td>
</tr>
<tr>
<td>Steggerda and Mitchell (120)</td>
<td>USA</td>
<td>13 young adults</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Outhouse et al (121)</td>
<td>USA</td>
<td>7 young men and women</td>
<td>662</td>
<td>10.7</td>
</tr>
<tr>
<td>McKay et al (122)</td>
<td>USA</td>
<td>124 college women</td>
<td>810</td>
<td>12.5</td>
</tr>
<tr>
<td>Patton and Sutton (123)</td>
<td>USA</td>
<td>9 young women</td>
<td>750</td>
<td></td>
</tr>
<tr>
<td>Hegsted et al (124)</td>
<td>Peru</td>
<td>10 adult men</td>
<td>200</td>
<td>3.3</td>
</tr>
<tr>
<td>Malm (14)</td>
<td>Norway</td>
<td>23 men</td>
<td>430</td>
<td>6.1</td>
</tr>
<tr>
<td>Nordin (117)</td>
<td>England</td>
<td>212 balances on 84 adults</td>
<td>578</td>
<td>8.4</td>
</tr>
<tr>
<td>Ackerman and Toro (125, 126)</td>
<td>USA</td>
<td>8 elderly men</td>
<td>1031</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 elderly women</td>
<td>923</td>
<td>16.7</td>
</tr>
<tr>
<td>Roberts et al (127)</td>
<td>USA</td>
<td>9 elderly women</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>Oblison et al (128)</td>
<td>USA</td>
<td>136 elderly women</td>
<td>830</td>
<td></td>
</tr>
<tr>
<td>Gallagher (129)</td>
<td>England</td>
<td>18 elderly women</td>
<td>1700</td>
<td></td>
</tr>
<tr>
<td>Heaney et al (89)</td>
<td>USA</td>
<td>41 postmenopausal women</td>
<td>1504</td>
<td></td>
</tr>
</tbody>
</table>

(131) studied normal postmenopausal women placed on a calcium supplement (yielding a total intake of approximately 1.5 g/day). Radiogrammetry (cortical thickness of three metacarpals) and photon absorptiometry of the distal forearm were used to measure change in bone mass. In the first study controls lost a significant quantity of bone as assessed by radiogrammetry, while those on calcium did not, and the difference between control and treatment groups was significant. Both untreated patients and those on calcium lost significantly as assessed by photon absorptiometry; and although the rate of loss on calcium was less than on placebo, the difference in rate between the two groups was not significant. In the second study the rate of change measured by photon absorptiometry in the ulna was significantly less for the calcium supplemented group than for controls, but the difference in the radius was not significant, although loss was slower in the calcium treated group. No significant changes were found by radiogrammetry, and the calcium treated group were found to be losing at a significant rate.

Nordin et al (44) studied bone loss in a population of patients with crush fracture osteoporosis. Forty-one patients served as controls; while 20 osteoporotics with normal calcium absorption received 1.2 g Ca/day for 1 yr. Changes in mean metacarpal cortical areas were calculated for the 2nd, 3rd, and 4th metacarpals of each hand. The weighted mean rate of change of cortical area for the calcium-treated group was only slightly negative and was not significantly different from zero. However, this group did not differ significantly from the untreated subjects who were losing bone at a significant rate.

Lee et al (132), using a radiodensitometric technique on the phalanges, studied the effect of calcium supplements (yielding a total intake of 1152 mg/day) in a population of 20 elderly (mean age 70) women and found a significant increase in 6 months. No controls were followed. Albanese et al (133), also using the radiodensitometric technique on the phalanges of 17 subjects (mean age 82), found a significant increase in mass over a 3-yr period relative to untreated controls, with a calcium supplement of 750 mg/day (total intake 1200 mg/day). Smith et al (99) followed a group of elderly females (age 81) for 3 yr using the photon absorption technique in the radius. An untreated group of 17 women lost bone while there was a positive slope in a calcium-treated group which was significantly different from the untreated controls.

The effect of supplementation of calcium carbonate (1.0 to 2.5 g/day) on subsequent vertebral fractures has been reported by Riggs et al (71). Among 44 untreated controls observed over 90 patient yr, there were 845 fractures per 1000 patient yr. Among 28 osteoporotics observed over 83 patient yr with
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calcium supplements, there were 398 fractures per 1000 patient yr, and these differences were significant. However, this study was not a prospective randomized trial.

By contrast with the foregoing, Christiansen et al (134) studied several therapeutic agents in a population of normal postmenopausal women using the photon absorption technique on the distal forearm. The placebo-treated group, in addition to all other participants, received 500 mg of supplemental calcium, and over the 2 yr of follow-up experienced a significant loss of bone (3.3%, p < 0.001). No untreated controls were followed. This study is not necessarily in conflict with the others cited, but it does suggest that a 500 mg supplement is not sufficient to retard age-related bone loss.

Very recently Thallasinos et al (135) have described long-term balance effects of calcium intakes in the range of 2.5 g/day. Observation in this study extended out to 10 yr in some cases, and averaged 3.5 yr. Mean balance was significantly more positive at the end of observation in nine typical osteoporotics than was observed on home diets containing an average of about 0.4 g Ca/day. These results are complicated by the concurrent use of estrogens for a major fraction of the treatment period; nevertheless this study represents the longest period of observation and the highest calcium intake reported to date.

Natural Intakes. Very few balance studies have been performed in individuals on their self-selected, home calcium intakes. Only the last two studies cited in Table 3 exhibit this feature. Heaney, et al (89) in 233 balances obtained on 150 estrogen-replete perimenopausal women observed a mean requirement (±SEM) of 990 ± 22 mg/day, and in 41 balances from estrogen deprived women of the same general age, a mean requirement of 1504 ± 115 mg/day. Gallagher (129) reached a similar conclusion in a smaller number of elderly subjects.

Comment. The reported prospective studies on the effect of calcium supplementation on bone loss in early postmenopausal women and those with clinical osteoporosis do not allow firm conclusions. In most cases numbers of patients studied were small, and follow-up was for 2 yr or less. Nevertheless, in all instances, when an untreated control group was included, those receiving calcium lost bone at a slower rate, although the level of significance was often not reached. It cannot be concluded from these studies how long this slower rate, if it is real, would persist. This is because application of the balance method may impose an important observational artifact that has not been sufficiently appreciated in the past.

Bone remodeling is a relatively slow process, and the time required to complete a cycle may be even slower with age (136). When calcium intake is experimentally manipulated (in order to observe balance performance at various intake levels), reflex changes in bone remodeling are produced which require 6 to 18 months to reach equilibrium. These remodeling changes produce both short-term changes in calcium balance and altered bone mass values detectable by modern techniques. The actual balance performance on various intakes (and the rate of change in bone mass) can be evaluated only when a new equilibrium state is reached. Few published treatment studies have extended beyond 2 yr of observation under high calcium intake regimens; hence long-term balance effects of high calcium intakes are largely unknown. Short-term treatment studies showing cessation (or reversal) of loss on calcium supplements may represent more a remodeling transient than a long-term steady-state.

In light of the remodeling response to alteration of calcium intake, the balance method and bone mass measurement can yield reliable results in only two circumstances: 1) when the duration of observation on a supplement extends to more than 2 yr (and preferably more than 3 yr); or 2) when the subjects are studied on their own self-selected, home intakes.

Only three published studies meet these criteria. In the one long-term study using quite high intakes, there was a consistent positive balance effect. And in the two studies reported in which women were studied on their customary intakes, relatively high mean intake requirements were found.

It is worth noting, as we conclude this section, that inconsistencies have appeared in past editions of "Recommended Dietary Allowances" of the Food and Nutrition Board (100, 137). Despite stressing the nature of an
“allowance,” (vide supra), the Board, in the section on calcium in the 1968 edition (137), pointed out “If osteoporosis is a reflection of calcium lack, the daily allowance of 800 mg for the adult female may well allow little margin of safety . . . .” These words are omitted from the 1974 (138) and 1980 editions and in their place are substituted mutually contradictory statements to the effect that low calcium intakes are sufficient to maintain calcium balance and that high intakes cannot prevent osteoporosis. It is pertinent simply to point out that all persons lose bone with age and that such loss is manifested as negative calcium balance. Thus, a person cannot develop osteoporosis and remain in calcium balance at the same time.

Finally, it must be reiterated that balance studies showing adaptation in some individuals at low intakes are not a secure base for estimating population requirements. This is both because no provision is thereby made, even in those who adapted, for recovery from periodic episodes of negative balance, and because there is evidence that zero balance is inadequate during early adult years.

Animal experiments. It is clear from studies in animals that isolated calcium deficiency results in a decrease in skeletal mass—a condition similar to osteoporosis, and not to osteomalacia. Evidence from a variety of species has been reviewed by Nordin (139). Low calcium diets result in loss of trabecular bone in adult cats (140), a generalized thinning of bone in dogs (141), a generalized decrease in bone mass in young growing rats (142). Jowsey and Gershon-Cohen (143) fed adult cats a low calcium diet for 20 wk and found decrease in skeletal weight, radiographic evidence of osteoporosis, and, on microradiographs, increase in bone resorptive surfaces. There was no evidence of osteomalacia. These changes could be partially reversed by administration of calcium. Griffiths et al (144) found in six rhesus monkeys fed a low calcium diet over several years that the radiographic and histological patterns were compatible with osteoporosis, and, on microradiographs, increase in bone resorptive surfaces. There was no evidence of osteomalacia. The calcium intake requirement for most animals is apparently substantially higher than for man. Heaney et al (150) have called attention to the fact that the RDA’s for animals ranging in size from 1 to 800 mg fit well a log-log relationship with body mass for all species except Homo sapiens, for whom the RDA is about one-fifth the predicted value (Fig 3). Even human populations consuming intakes of 1.0 to 1.5 g/day would be clearly deficient by such a standard, and thus the possibility must be considered that the epidemiological evidence cited is dealing not with deficiency versus repletion, but with varying degrees of deficiency. On the other hand, protein requirements of man are also lower than would be predicted from those of other species, and it is likely that both differences are due in some part to relative differences in growth rate between man and animals. Additionally, it must be said that the scientific basis for the animal RDA’s is somewhat weak and that interspecies differences by dietary calcium deprivation or by castration is enhanced in rats by the provision of a high calcium diet and/or calcitriol (or 1-α-hydroxy vitamin D) (145, 146). However, there is not yet available in any experimental animal a model of age-related bone loss which faithfully mimics human osteoporosis or any of the likely pathogenetic models. The possibility of developing one such model is suggested by the discovery that elderly rats develop reduced renal secretion of calcitriol which cannot be reversed entirely by the administration of exogenous parathyroid hormone (147, 148). It is of considerable interest that estrogen treatment of estrogen-deficient animals or estrogen-deficient humans increases the serum levels of calcitriol and increases the efficiency of intestinal calcium absorption (42). However, it is still not entirely clear whether these two events are causally linked, because estrogen treatment increases the concentration of serum binding proteins for calcitriol and does not increase the serum concentration of the free hormone (149). Until it becomes clearer whether free or total calcitriol is the clinically and biologically significant serum measurement to concentrate on, the results of these estrogen repletion experiments will remain susceptible to multiple interpretations.
in digestive systems (and hence in the bioavailability of ingested calcium) make extrapolation from animals to man hazardous.

In summary, it is apparent that calcium deficiency can, in adult animals, produce bone loss and, in growing animals, a failure of bone growth. Grossly and by traditional histology, the bones appear to be osteoporotic. Few detailed studies of the bone histology have been performed and none has used modern techniques of histomorphometry. In addition, none of the animals studied developed spontaneous fractures. The relevance of these experiments to human disease is unknown.

**Comment**

The requirement for calcium in the elderly remains controversial, although more recent evidence points in the direction that the requirement may be higher than previously thought. This evidence comes from several sources, reviewed in detail in the foregoing, and can be summarized briefly as follows. Studies performed in actual elderly subjects (as contrasted with young adults) have uniformly revealed mean intake requirements for calcium balance above the current RDA for the United States (and hence allowances higher still). Further, calcium supplementation in the elderly has produced some degree of slowing of age-related bone loss, calcium balance improvement, or decrease in fracture prevalence. Essentially all published reports agree in these respects.

Controversy continues to surround this issue principally because most of the world's population ingests less calcium than the RDA for the US and is nevertheless manifestly able to grow and form a skeleton satisfactory for ordinary adult function. This apparent contradiction appears to be explained by several recent observations and insights reviewed in the foregoing sections. First calcium absorption efficiency declines with age, and hence an intake adequate to grow a skeleton may not be adequate to maintain it. Second there are now recognized to be important differences between lesser developed countries and industrialized nations which make comparison of calcium intake requirements hazardous. These differences include lower protein intakes and heavier mechanical loading in lesser developed countries, both of which favor calcium retention. Additionally, ethnic differences between populations in lesser developed countries and industrialized nations (e.g., larger skeletons in African Blacks and their descendents) imply a genetic basis for differences in efficiency of calcium utilization. Third, only recently have we begun to realize that all persons lose bone with age and that peak bone mass achieved at age 30 to 35 is an important determinant of fracture risk 40 or more yr later. Thus, since bone mass normally continues to increase until age 30 to 35, an intake found to be sufficient to maintain zero balance in young adults can no longer be considered to provide adequate nutrition. Some degree of positive balance, as during the years of linear growth, is the criterion of adequacy until age 30 to 35. Current knowledge does not permit us to define either what that degree of positive balance ought to be, or the extent to which peak adult bone mass can be influenced by calcium intake in the early adult years.

**Health implications of calcium deficiency in the elderly**

Calcium deficiency, to the extent that it is related to the pathogenesis of osteoporosis, has important implications for the health of aging Americans. Osteoporosis produces dis-
ability because of fractures, particularly of the vertebrae, distal radius, and hips, which are the hallmarks of the disease. In the United States, 5.3% of all patients over age 65 discharged from hospitals have the diagnosis of fracture, and this increases to 10.2% after age 85. At age 85 and older, nearly 4% of the population sustains a serious fracture each year (151). The cost is enormous, over one billion dollars per year for hip fractures alone (152), in addition to the suffering, physical disability, and mortality associated with the disease.

It is generally assumed that fractures which occur with osteoporosis are related to a decrease in the quantity of bone present (153). However, other factors, intrinsic or extrinsic to the skeleton, may also play a role in fracture pathogenesis (154). These could include other disease processes, such as osteomalacia (see “Vitamin D and bone health in the elderly” p 1014), abnormalities of bone remodeling, neuromuscular disease leading to a tendency to fall, and the frequency and degree of trauma. Nevertheless, low bone mass must be a major contributing cause of fracture (155, 156). As has been seen, calcium deficiency may play a role in the determination of bone mass; it probably has little effect on the other contributing factors.

The amount of bone remaining in the elderly skeleton is determined by two factors: 1) the quantity present at maturity, and 2) the subsequent rate of loss. Bone mass at maturity is, in part, genetically determined, but a multitude of environmental factors, from placentation, to exercise, to calcium intake, may also play a role (5, 157). Subsequent rates of bone loss are also probably multiply determined, by estrogen levels, physical activity, and effective calcium intake.

There is an increasing body of evidence that there are at least two distinct fracture syndromes represented within the designation “osteoporosis”: The vertebral crush fracture syndrome and the upper femoral fracture syndrome, each with different patterns of cortical and trabecular bone loss. (See Appendix 3). Riggs et al (158) have recently shown that vertebral crush fracture patients exhibit vertebral bone mass values distinctly lower than age-matched nonosteoporotic persons; by contrast hip fracture patients exhibit hip bone mass values well within the normal range for their age. In brief, crush fracture patients appear to represent a distinct, pathological subset of women; whereas hip fracture patients appear to be reaping the consequences of the age-related bone loss which affects all persons of the same age. The relation of calcium nutrition to these two syndromes may well be quite different. It is worth noting again that the protective effect of high calcium intake observed in the Yugoslav study cited earlier (109) was on hip fracture rates, and that no differences were noted for wrist fractures. (Spine fracture rates were not measured.)

Potential toxic effects of high intakes of calcium in the elderly

Within the range of probable calcium intakes, calcium exhibits very little of what could be considered toxic manifestations. The principal side effects from excessive intake of calcium are hypercalcemia, hypercalciuria, urinary tract calculi, calcification in a variety of soft tissues, notably in the kidney and in arterial walls, and suppression of bone remodeling.

An FDA panel, which in 1979 reviewed the data on safety and effectiveness of a considerable number of nutrients, concluded that “calcium intakes ranging from 1,000 to 2,500 mg daily do not result in hypercalcemia in normal individuals” (159).

Hypercalciuria

As noted in Appendix 2, the response of urinary calcium to changes in calcium intake is modest, so that 24-h urinary calcium excretions above 300 mg do not occur in normal individuals except at very high calcium intakes (160). For each 1 g of calcium increase in the intake, the 24-h excretion of calcium in the urine increases on the average by less than 70 mg in middle-aged and elderly women (22, 115, 161). Absorptive hypercalciuria is much less likely to be found in the elderly than among young adults. There are a number of conditions, however, in which increased intestinal absorption of calcium often occurs with resultant hypercalcemia and hypercalciuria. One of these is hyperparathy-
roidism, the prevalence of which is approximately 1 to 2 per 1000 in the population over 63 yr of age (162). Other disorders in this class, though uncommon, certainly so in the elderly, are sarcoidosis and other granulomas such as tuberculosis, with an associated increased sensitivity to vitamin D and its metabolites (163, 164). Hypercalcemia is possible in high calcium treatment of hypoparathyroidism and in parenteral hyperalimentation (163).

Urinary calculi

Development of urinary calculi in connection with high calcium intakes is rare. Robertson et al (165), in an analysis of dietary changes and the incidence of urinary stones in the UK between 1958 and 1976, found no correlation between hospital discharge diagnoses of urinary calculi and dietary intake of calcium, oxalate, phosphate, magnesium, refined carbohydrate, and total protein; the only association detected was with the intake of animal protein. In a series of 200 patients with peptic ulcers compared with 200 controls (166); renal stone incidence in the ulcer group was 7 versus 1% in the controls; the report states that the ulcer patients consumed “large quantities of milk,” but the report is suggestive of milk-alkali syndrome, to be discussed below; no mention was made in this report of nephrocalcinosis or other extraosseous calcification.

Calcium sensitivity in chronic renal disease

Possibly the clearest examples of calcium toxicity may be seen in patients with chronic renal disease undergoing dialysis. This is a situation in which controls over calcium ingress and egress may be immobilized. Under such circumstances the amounts of calcium entering the body are critical. Renal osteodystrophy may occur either in the form of osteitis fibrosa or osteomalacia, or, if oral calcium administration be too great or the level of calcium concentration in the dialysis bath too high, as hypercalcemia and/or extraosseous calcification (167, 168). The concentration of calcium in the dialysis bath is critical: too low a level protects against soft tissue calcification at risk of bone rarefaction, and too high the reverse. The least likelihood of net transfer of calcium or change in plasma calcium level in a normocalcemic patient is probably produced with a dialysate concentration in the range of 5.8 to 6.2 mg/100 ml (167).

Milk-alkali syndrome

Patients with peptic ulcer have long been known to be susceptible to abnormalities in calcium metabolism in association with the intake of very large amounts of calcium along with absorbable alkali. Burnett et al (169) described the chronic form of “milk-alkali syndrome” in 1949 in a group of patients under treatment for ulcer for 2 to 30 yr with daily consumption of 2 to 5 quarts of milk and quantities of antacids, usually NaHCO₃; the pertinent findings were elevated serum calcium (usually 12 mg/dl or greater), mild alkalosis, nephrocalcinosis, and band keratopathy. Intermediate and an acute forms of the syndrome have been described, and in 1965, McMillan and Freeman (170) studied the latter by administration to patients of 1 to 1.5 l of milk and an average of 28 g of calcium carbonate per day for 7 days, versus the same quantity of milk with 120 ml/day of aluminum hydroxide. On these extremely high doses of calcium carbonate (amounting to 11.2 g Ca, plus more than another gram in the milk), there was a 19% decrease in creatinine clearance, a brief fall in phosphate clearance, a rise in serum calcium to an average of 11.2 mg/100 ml and a slight increase in urinary calcium. Lee et al (163) have more recently summarized the characteristics of the three forms of the milk-alkali syndrome. Punzar and Somer (171) reviewed the field in 1963 and found that hypercalcemia had been reported on milk intakes as low as 1.9 to 2.7 l/day, so long as absorbable alkali (sodium bicarbonate) was ingested in large quantities.

Isotopic studies in patients with hypoparathyroidism showed that administering 10 to 18 g of absorbable alkali per day (alone or together with calcium carbonate) decreased the size of both fast and slow exchanging calcium compartments and reduced the rate of calcium deposition in bone (172). In one normal control subject, sodium bicarbonate alone produced this same effect.

As calcium carbonate has supplanted sodium bicarbonate as a more commonly used antacid, additional studies have been made...
of its metabolic effects (172) and absorption (173). Ivanovich et al (173) in studies of absorption with $^{45}$Ca noted that with single doses of 4 g (1.6 g Ca), hypercalcemia did not occur in any patient, but did so in most patients at intakes of 8 and 12 g. Calcium carbonate was absorbed approximately as well as the gluconate, making allowance for differences in carrier load (173). However in a small number of patients with achlorhydria absorption ranged from 0 to 2%. While it is not possible to predict with certainty which patients will, over a long period of time, develop signs of the milk-alkali syndrome, it seems clear that it is not likely to occur in the absence of systemic alkalosis. The syndrome can be expected, however, when high doses of calcium are given with sodium bicarbonate, or when calcium carbonate alone is given in doses of 24 g/day or more. Hypercalcemia is most unlikely at doses often suggested in the management of osteoporosis, ie, up to 2.5 g/day calcium in divided doses. The role of the anion in producing hypercalcemia remains largely uninvestigated.

Remodeling suppression

High calcium intakes have been widely reported to suppress bone remodeling (eg, Reference 130), relative to levels found at usual calcium intakes. This suppression is probably related to suppression of endogenous PTH release, and is a consequence of the fact that PTH is the principal activator of remodeling in the adult skeleton. A certain amount of bone remodeling is believed to be necessary for periodic renewal of the aging bony material and for repair of microfractures. If remodeling were suppressed below the optimal level for these reparative functions, bone fragility could increase irrespective of changes in mass. However when parallel studies have been performed in postmenopausal women, remodeling suppression by calcium has always been of the same general magnitude as suppression by estrogen, and in no series has an average reduction in remodeling greater than 50% been reported. No data exist as to whether this degree of suppression is harmful or whether high intakes in general can override the intrinsic reparative impetus of a microfracture.

Summary

Calcium intakes up to 2.5 g/day do not result in hypercalcemia or other untoward effects in normal individuals, including the elderly. Urine calcium increases on the average less than 70 mg/day for each 1 g increase in calcium intake. Hypercalcemia may occur, however, in hyperparathyroidism, sarcoidosis, and with high calcium intakes in the treatment of hypoparathyroidism and in parenteral hyperalimentation. Urinary calculi in association with hypercalcemia and a decrease in renal function may occur with the combination of high calcium intake and absorbable alkali (as in "milk-alkali syndrome" or with doses of calcium carbonate providing approximately 10 or more g of elemental calcium). In the management of chronic renal disease, calcium intake by mouth and calcium transfer from dialysis bath are critical, too low a level of calcium increasing susceptibility to bone rarefaction, and too high, increasing susceptibility to soft tissue calcification. Some degree of remodeling suppression occurs with high calcium intakes. While this effect clearly slows bone loss, it might also slow repair of microdamage. This latter outcome remains only a theoretical possibility.

Important issues requiring further investigation

Effect of dietary calcium manipulation on rate of age-related bone loss

While some portion of age-related bone loss is associated with decreased mechanical loading of the skeleton with age, there is a now fairly large body of evidence that suggests that this rate of loss can be accelerated by effective calcium deficiency and retarded by calcium supplements. The true extent to which age-related loss can be retarded urgently needs study. Duration of treatment must be long enough to allow for the unavoidable remodeling transients, and to permit measurement of rates of loss at the new remodeling equilibrium of the skeleton. Optimal calcium intake required to produce this effect needs to be determined.

Effective absorption of high calcium intake loads in the elderly

Although it is clearly established that intestinal absorption efficiency for calcium de-
clines with age, the actual extent of the decreased transport capacity is unknown, particularly under relatively high load conditions. Further studies are needed both of effective absorption under load and of factors that may promote or retard absorption (such as gastric acid production).

Role of calcium intake early in life in determining peak adult bone mass

As noted earlier, peak bone mass is not achieved until sometime in the 4th decade of life. Apart from studies of nutrition during linear growth, essentially no data exist that bear directly on the relation of calcium intake to development of peak bone mass. Because of its potential importance this question needs immediate and concerted study.

Role of peak adult bone mass in determining fracture susceptibility in the elderly

To date only cross-sectional studies bear on the relation of peak mass in the 4th decade to susceptibility to fractures in the 7th to 9th decades. Because of the potential importance of this issue, particularly in terms of early nutritional prophylaxis of osteoporosis, attention should be directed toward developing the most efficient possible study design, and suitable prospective studies should be begun without delay.

Miscellaneous nutritional physiological issues

Given the low absorption of calcium in general and the further decline in the elderly, bioavailability of calcium from different food sources and supplements needs to be determined by modern techniques. The relative efficiency of calcium utilization and retention from different food sources (with varying loads of other nutrients) needs further exploration. Additionally uncertainties concerning the physiological effects of high calcium intakes on absorption, on the calcium-homeostatic system, and on bone remodeling, need to be resolved. Finally the effect of the associated anions in the various available calcium supplements needs careful study.

Therapeutic trial of calcium supplements in the elderly

Prevention is both more important and more effective than treatment. Nevertheless there exists evidence to suggest that the large group of already, or soon to be, osteoporotic individuals might be helped by calcium supplements. This possibility is worth a large-scale, multicenter trial, with fracture the endpoint, and with careful attention to measurement of effective calcium absorption. Hip and spine fracture endpoints should be separated in study design.

Age- and sex-specificity of RDA

The notion of a single value for the RDA for all adults (exclusive of pregnancy and lactation) implies that interindividual variation in mean requirement is not a function of age or sex. Evidence suggests instead that the mean requirement shifts systematically with age in both sexes, and in women, at menopause. Attention should be directed toward development of age- and sex-specific standards.

Summary

The average elderly person is in negative calcium balance and accordingly is losing bone mass. While factors such as decreased mechanical loading of the skeleton undoubtedly figure in this age-related loss, a growing body of evidence suggests that inadequate calcium intake may contribute to this loss. On any given day men and women in the US 65 yr or older ingest about 600 and 480 mg calcium, respectively. Calcium intake in the elderly is less than in the young, and reduced absorption efficiency further lowers effective intake. Additionally, other nutrients such as protein and fiber, taken in excess, effectively increase the calcium requirement. Estrogen withdrawal at menopause leads to a decrease in intestinal calcium absorption efficiency and in renal calcium conservation, both effects equivalent to an effective increase in calcium intake requirement.

Thus it is not surprising that all studies of mean requirements for zero balance performed in elderly subjects have yielded values above the current RDA for the US. The available evidence thus suggests that the RDA for adults should surely not be lowered below its current level (800 mg), but that, instead, it ought to be raised. It is not possible to say with certainty to exactly what level, but available evidence is compatible with allowances of at least 1200 to 1500 mg/day.
Further, the evidence indicates that the mean requirement ought to be thought of as a complex function of age, sex, absorption efficiency, intake of protein, fiber, and probably other nutrients, estrogen status, and mechanical loading. Extensive experience with calcium supplements indicates that daily intakes up to at least 2.5 g of elemental calcium are quite safe in all persons except for certain subsets of the population uncommon among the elderly (e.g., those with sarcoidosis, active tuberculosis, or other absorptive hypercalciuric syndromes).

At the same time it must be said that osteoporosis is a complex, multifactorial disorder, and that factors unrelated to calcium nutrition undoubtedly play important, even dominant roles in many—perhaps most—osteoporotics. The available evidence, taken together, does not indicate that raising calcium intake will abolish the problem of osteoporosis. It does indicate, however, that calcium nutrition is considerably more important in the genesis of osteoporosis than has been commonly thought for the past 35 yr. As our listing of “important issues” indicates, the full extent of that importance, in both pathogenesis and prophylaxis, remains to be elucidated. In the meanwhile we believe that the balance of risks and benefits involved in a general increase in calcium intake clearly favors some degree of upward adjustment of both the RDA and some change of calcium fortification policies for basic food stuffs.

Appendices

Appendix 1. Bone consolidation after growth

The character and magnitude of bone consolidation during the postgrowth phase is illustrated in Figure 4, constructed from data of Garn (103). Medullary cavity width in long bones expands during growth and reaches an early maximum at the end of the most rapid phase of bone dimensional growth (ca age 12 in the female, age 15 in the male). Net bone apposition occurs on the endosteal surface for the next 15 to 20 yr, so that medullary width contracts and reaches a minimum—and hence bone mass a maximum—at about age 30 to 40. During the same period, cortical porosity decreases as well, so that positive balances obtain at all the osseous envelopes.

From that point onward bone loss ensues, with loss at the endosteal-trabecular envelope predominating. Figure 4 illustrates the predominantly endosteal character of both the early consolidation and the later loss, and graphically demonstrates also the very considerable sexual dimorphism after age 50.

The question must be raised whether calcium intake may be a limiting factor in the increase in skeletal mass which occurs after growth has ceased, but before age-related loss begins. It has been shown that medullary width is excessively large in cases of gross malnutrition (103), and calcium deficiency alone has been shown to produce a clinical syndrome resembling rickets, even in the presence of adequate vitamin D (174). The effect of less severe variations in calcium intake on peak bone mass development has yet to be evaluated.

Appendix 2. Relationship between intake, fractional absorption, and endogenous calcium excretion

It is well recognized that fractional absorption falls as intake rises. The relationship is probably curvilinear, especially at low intakes, but across the more usual intake range can be adequately approximated by a straight line. In perimenopausal women this linear relationship has been observed (154) to be given by

\[ Y = -0.1008X + 0.3362 \pm 0.06783, \]
where \( Y = \) fractional absorption and \( X = \) calcium intake (in g).

The value of the regression coefficient is such that, with increasing intake, the decrement in fractional absorption is not as great as the increment in absorbed intake. Hence absolute absorption rises as intake rises, even though absorption efficiency falls. (As a concrete example, the foregoing equation indicates the absorption is 28.6% at a 500 mg intake, and falls to 23.5% at a 1000 mg intake. At the lower intake, 143 mg is absorbed, and at the higher intake, 235 mg.)

Endogenous loss consists of fecal and urinary components. Both increase as calcium intake rises. In several large studies in middle-aged and elderly persons (22, 49, 175) the slope of urine calcium on intake is on the order of +0.05 to 0.07, ie, urine calcium increases by 50 to 70 mg for every 1 g increase in dietary intake. As noted elsewhere, urine calcium is notably influenced by such other dietary components as phosphorus and protein.

Endogenous fecal calcium represents calcium secreted into the intestinal tract (or sloughed off as mucosal detritus), mixed to some extent with dietary calcium, and then partially reabsorbed. Hence the endogenous fecal calcium consists of the unabsorbed component of all the calcium which enters the gastrointestinal tract from endogenous sources. Abundant evidence indicates that this secreted material is subject to reabsorption to a great extent like diet (175) (Heaney RP, unpublished observations). Hence fractional absorption of secreted intestinal calcium varies inversely with dietary intake just as does fractional absorption of intake calcium. There is evidence that calcium intake does not itself affect the amount of intestinal calcium secretion (49, 175). On the other hand phosphorus intake does increase intestinal secretion of calcium (see above) (49). Thus endogenous fecal calcium increases as both calcium and phosphorus intakes rise, although for different reasons; the effects of the two agents are independent and additive.

Appendix 3. Bone mass measurement

The techniques used for bone mass measurement include radiogrammetry, photon absorptiometry, x-ray photodensitometry, and computerized tomography. Radiogrammetric measurements can be performed quite precisely, especially if multiple metacarpals are measured, but they do not very accurately reflect the amount of bone present (176, 177). This technique measures changes on the endosteal and periosteal surfaces, and not on the Haversian envelope. In addition, the correlation between these morphometric measurements and total skeletal mass as determined by neutron activation is weak (178). Nevertheless, such measurements are probably valid indices of changes in skeletal mass in large studies, since loss of cortical bone in the metacarpals is likely to be associated with loss elsewhere, although relative loss may be quantitatively different from site to site.

Photon absorptiometry is both precise and accurate (179) and generally correlates well with total skeletal mass (178), except that correlation is not as strong in patients with osteoporosis. This technique measures net change on all envelopes, periosteal, Haversian, and endosteal, but does not distinguish between them. If loss or gain of bone were, in part, due to change in Haversian porosity, as it is in bone growth and age-related loss, it would be detected by this technique but not by radiogrammetry. Photodensitometry can be precise and accurate, but must be performed under rigorously controlled conditions. In practice it is often not as valid as the other methods (179).

Two techniques have been used to measure changes of bone mass in the vertebrae. Dual energy photon absorptiometry (180) measures change in the entire vertebra, both cortical and trabecular bone. Computerized tomography (96) can be used to measure the trabecular bone within vertebral bodies. Under proper circumstances, the latter technique is very precise for repeated measurement, but accuracy is adversely affected by a reciprocal change in marrow fat content.

It is essential in determining rates of change in bone mass that measurements be made at frequent intervals over sufficiently long periods of time (181). This is particularly true where rate of change is very small, as in age-related bone loss. An adequate control group must be included if the effect of therapeutic intervention is to be determined. Different individuals lose at quite different rates
(154), and an experiment can be biased, especially if the numbers are small, if by chance alone a group of all rapid or all slow losers is chosen.

Current evidence suggests the patterns of loss for cortical and trabecular bone may differ. Riggs et al (180), using the dual photon technique, have found that bone was lost from the spine in a linear fashion beginning in the 3rd decade. This technique measures the total quantity of bone in the spine, not trabecular bone alone. Arnold (182) measured trabecular bone concentration in vertebrae obtained at autopsy and also found a linear decrease starting at the 3rd decade. Meunier et al (183), studying trabecular bone volume in iliac crest biopsies, found slight loss starting in the 3rd decade, with markedly accelerated loss in the 6th decade. Cann et al (184), using the CT technique, found rapid loss from the spine after menopause. It is not apparent which model is correct for the spine, but loss of bone apparently starts early, and, in addition, there may be accelerated loss after menopause. Cortical bone loss measured in the periphery may start slowly in the 5th decade (103), but there is more rapid loss after age 50 which follows an exponential pattern (154). Thus, trabecular bone loss may follow a somewhat different pattern than cortical bone loss, and the radiogrammetric techniques used in epidemiological studies would not detect changes in trabecular bone at all.

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