Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships:

3. Calcium and Osteoporosis

December 1991

By

Robert P. Heaney, M.D.

Prepared for

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20204

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LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon literature reviews and the scientific analyses by knowledgeable investigators engaged in work in specific areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA), in accordance with the provisions of Task Order #9 of Contract No. 223-88-2124. Potential authors and reviewing consultants were identified by the LSRO based on their qualifications, experience, and freedom from conflict of interest, with due consideration for balance and breadth in appropriate disciplines. The author and reviewing consultants were selected with the concurrence of the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB).

On March 14, 1991, the FDA requested submission of scientific data and information on the ten specific topics for which health claims might be made (Federal Register 56:12932-12933). The scientific data and information provided in response to this request were considered by LSRO in preparing this report. Copies of the submitted materials are available for public inspection at the Dockets Management Branch, FDA (Docket No. 91N-0094). Copies of documents cited in this report are available for public inspection at LSRO, FASEB.

Robert P. Heaney, M.D., John A. Creighton University Professor, Creighton University, Omaha, NE, should be cited as the author of this report. The LSRO acknowledges the efforts of Robert P. Heaney, M.D. and also the critical assistance of Claude D. Arnaud, Jr., M.D., Professor of Medicine and Physiology, University of California, San Francisco, CA; and Lawrence G. Raisz, M.D., Professor of Medicine, and Head, Division of Endocrinology and Metabolism, University of Connecticut Health Center, Farmington, CT, who reviewed several drafts of the manuscript. The appendix tables were prepared by the LSRO staff and author and were critically reviewed by the author and reviewers. Subsequently the draft report and tables were revised by the author, edited by the LSRO scientific staff, and received final concurrence from the author and reviewing consultants.

The evaluation of scientific literature, data, and information submitted to the LSRO was made by the author, reviewers, and the LSRO independently of FDA or any other group, governmental or non-governmental. The author and LSRO accept responsibility for the accuracy of the report conclusions and its appendix table(s). This final report was reviewed and approved by members of the LSRO Advisory Committee under authority delegated by the Federation Board. The LSRO Advisory Committee members who reviewed this report were free of conflicts of interest in regard to the subject matter under policies established by the Federation. Upon completion of these review procedures, the report was approved by the Executive Director, FASEB, and transmitted to FDA.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

December 31, 1991
Date

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
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I. STATUS OF SCIENTIFIC OPINION AS OF APPROXIMATELY 1988

A. SUMMARY OPINION FROM BENCHMARK DOCUMENTS

Eight benchmark documents reflect prevailing scientific opinion as of approximately 1988 (Table 1). One of these, "Osteoporosis: Cause, Treatment, and Prevention" (U.S. Department of Health and Human Services, 1986), is explicitly based on the 1984 NIH Consensus Development Conference (Consensus Conference, 1984). The report of this conference is therefore added to the list in Table 1 and its pertinent comments included among the following summaries.

As will be developed in greater detail in a subsequent section of this report, the relationship of calcium intake to osteoporosis can be summarized under four headings:

- development of peak bone mass;
- maintenance of acquired bone mass;
- protection against low trauma fractures; and,
- pregnancy and lactation.

Additionally, some of the documents state explicitly certain critical assumptions. Others express concerns about possible harm associated with overconsumption of calcium.

Pertinent statements from the benchmark documents are organized by these topics in the following paragraphs.

1. Development of peak bone mass

There is general agreement among the documents to the effect that achieving peak bone mass is a good, and possibly the best known, preventive against late-life osteoporosis. The documents further recognize the key role played by an adequate calcium intake during the first 30 to 35 years of life. Some call specific attention to calcium intake in female adolescents, which is characterized in those documents as "deficient".

- "If a young woman achieves a high peak bone mass -- possibly through increased calcium intake ... she may be less likely to develop osteoporosis later" (U.S. Department of Health and Human Services, 1986).

- "Presumably, persons with greater bone mass in early adulthood are able to resist the effects of age-related bone loss." "Although current epidemiologic and clinical evidence is uncertain, chronic low calcium intake may decrease peak bone mass, especially during adolescence." "Adolescent girls and adult women should increase consumption of foods high in calcium, including low-fat dairy products" (U.S. Department of Health and Human Services, 1988).

- "If there is insufficient dietary calcium during bone formation, linear growth will be impeded and peak bone mass may not be achieved" (National Research Council, 1989a).
Table 1. Benchmark Documents

Osteoporosis. Report of the 1984 Consensus Development Conference on Osteoporosis
(Consensus Conference, 1984)

Osteoporosis: Cause, Treatment, Prevention
(U.S. Department of Health and Human Services, 1986)

The Surgeon General's Report on Nutrition and Health
(U.S. Department of Health and Human Services, 1988)

Diet and Health: Implications for Reducing Chronic Disease Risk
(National Research Council, 1989a)

Recommended Dietary Allowances
(National Research Council, 1989b)

Proceedings of the National Conference on Women's Health Series —
A Special Topic Conference on Osteoporosis
(Food and Drug Administration, 1989)

Nutrition During Pregnancy
(Institute of Medicine, 1990)

Nutrition and Your Health: Dietary Guidelines for Americans, 3rd ed.
(U.S. Department of Agriculture and U.S. Department of Health and Human Services, 1990)

Healthy People 2000: National Health Promotion and Disease Prevention Objectives
(U.S. Department of Health and Human Services, 1991)
"... the most promising nutritional approach to reduce the risk of osteoporosis in later life is to ensure a calcium intake that allows the development of each individual's genetically programmed peak bone mass during the formative years... with special attention to intakes throughout childhood to age 25 years." The 1989 RDA recommends "an extra calcium allowance to permit full mineral deposition through age 24 rather than through age 18 years, as in previous editions of the RDA... An intake of 1,200 mg is recommended for both sex groups from ages 11 to 24 years" (National Research Council, 1989b).

"Calcium is important during growth, and probably up to about age 35, when peak bone mass is finally achieved." "The assumption that deficient peak bone mass attainment in adolescent females may contribute to subsequent postmenopausal osteopenia appears quite reasonable, although data supporting such an assumption remain preliminary. The current data indicate that calcium intake is deficient in the adolescent female. Also, in spite of the conflicting data in this area, the hypothesis of improving peak bone mass with increasing calcium intake remains tenable, and a 1,200 mg per day intake in adolescent females appears justified" (Food and Drug Administration, 1989).

"Diets of some groups of people are notably low in some nutrients. Many women and adolescent girls need to eat more calcium–rich foods, such as milk and milk products, to get the calcium they need for healthy bones throughout life" (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 1990).

"Calcium is essential for the formation and maintenance of bones and teeth. The level of bone mass achieved at skeletal maturity (peak bone mass) is a factor modifying the risk for developing osteoporosis. . . . Peak bone mass appears to be related to intake of calcium during the years of bone mineralization. . . . Most of the accumulation of bone mineral occurs in humans by about 20 years of age. However, after the linear growth phase, there is a period of consolidation of bone density that continues until approximately age 30 to 35. A high peak bone mass is thought to be protective against fractures in later life." One Health Status Objective specifies "Increase calcium intake so at least 50 percent of youth aged 12 through 24 and 50 percent of pregnant and lactating women consume 3 or more servings daily of foods rich in calcium, and at least 50 percent of people aged 25 and older consume 2 or more servings daily." "Osteoporosis is a multifactorial, complex disorder, but low calcium intake appears to be one important factor in its development. The ideal level of calcium intake for development of peak bone mass is unknown, and it has not been established to what extent increased calcium intake will prevent osteoporosis. However, females, particularly adolescent and young adult females, should increase food sources of calcium" (U.S. Department of Health and Human Services, 1991).

2. **Maintenance of achieved bone mass**

In general, the documents recognize a continuing need for calcium even after peak bone mass has been achieved. Some cite evidence indicating that a portion of age–related bone loss can be reduced or prevented by high calcium intakes, and some even suggest that the current RDA is too low.
"A number of risk factors for osteoporosis have been identified. These include: . . . a chronically low calcium intake" (U.S. Department of Health and Human Services, 1986).

"Prevention of fracture in susceptible patients is the primary goal of intervention. Strategies include . . . adequate nutrition including an elemental calcium intake of 1,000 to 1,500 mg/day . . . ." "Calcium deficiency has been implicated in the pathogenesis of this disease. . . . Among the many possible causes of primary osteoporosis, current data point to two: deficiency of estrogen and deficiency of calcium. . . . The following observations support a causal relationship between calcium deficiency and osteoporosis: calcium deficiency in experimental animals causes osteoporosis, a low calcium intake is common among the elderly in the United States, and calcium supplementation reduces bone loss. . . . Calcium metabolic balance studies indicate a daily requirement of about 1,000 mg of calcium for premenopausal and estrogen-treated women. Postmenopausal women who are not treated with estrogen require about 1,500 mg daily for calcium balance. Therefore, the RDA for calcium is evidently too low, particularly for postmenopausal women, and may well be too low in elderly men. In some studies, high dietary calcium intake suppresses age-related bone loss and reduces the fracture rate in patients with osteoporosis. It seems likely that an increase in calcium intake to 1,000 to 1,500 mg/day beginning well before the menopause will reduce the incidence of osteoporosis in postmenopausal women. Increased calcium intake may prevent age-related bone loss in men as well" (Consensus Conference, 1984).

"Many scientists believe that a chronic shortage of dietary calcium is one important factor leading to osteoporosis . . . . If these (calcium) losses are not balanced by adequate amounts of calcium in the diet, . . . bones begin to break down to supply the body's need for the mineral in maintaining the proper blood level of calcium." ". . . adult women and probably men should have a total daily intake of 1,000 mg of calcium, and women past menopause, not on estrogen therapy, need 1,500 mg daily" (U.S. Department of Health and Human Services, 1986).

"Published reports have shown either no relationship or only a modestly positive relationship between dietary calcium and cortical bone mass." "There is strong evidence . . . that calcium supplementation has a modest influence on preventing cortical bone loss. The evidence relating calcium supplementation to fracture prevalence is scanty" (National Research Council, 1989a).

"Metabolic, epidemiologic, and intervention studies are internally consistent, and indicate that inadequate calcium intake also makes an important contribution to involutional bone loss" (Food and Drug Administration, 1989).

"But some people do not get recommended amounts of a few nutrients, especially calcium and iron" (U.S. Department of Health and Human Services, 1990).

3. Protection against low trauma fractures

The only recognized clinical significance of osteoporosis lies in the tendency to low-trauma fractures. The benchmark documents generally recognize this fact; five of them cite evidence or summarize prevailing opinion to the effect that a low calcium intake increases risk of such fractures.

"How can osteoporosis be prevented and treated? . . . ." "Although complete proof is lacking that the other measures -- such as increased calcium intake -- prevent bone loss leading to
fractures, many believe that current data are sufficient to suggest that these measures be adopted" (U.S. Department of Health and Human Services, 1986).

- "Prevention of fracture in susceptible patients is the primary goal of intervention. Strategies include ... adequate nutrition including an elemental calcium intake of 1,000 to 1,500 mg/day . . . ." "In some studies, high dietary calcium intake suppresses age-related bone loss and reduces the fracture rate in patients with osteoporosis. It seems likely that an increase in calcium intake to 1,000 to 1,500 mg/day beginning well before the menopause will reduce the incidence of osteoporosis in postmenopausal women. Increased calcium intake may prevent age-related bone loss in men as well" (Consensus Conference, 1984).

- "A number of risk factors for osteoporosis have been identified. These include: . . . a chronically low calcium intake" (U.S. Department of Health and Human Services, 1986).

- "Although low calcium intake is associated with a higher frequency of fractures, . . . the potential benefits of calcium intakes above the RDAs to prevent osteoporosis . . . are not well documented and do not justify the use of calcium supplements." "The evidence relating calcium supplementation to fracture prevalence is scanty" (National Research Council, 1989a).

4. **Pregnancy and lactation**

The special needs of pregnancy and lactation are addressed chiefly in two of the documents.

- "This evidence suggests it is prudent to recommend a calcium intake of 1,200 mg throughout pregnancy and lactation, irrespective of age" (National Research Council, 1989b).

- "... on average, pregnant women ... were less likely to have met their RDAs for vitamins B6, D, E, and folacin; iron; calcium; zinc; and magnesium. ... the *Report on Nutrition Monitoring in the United States* ... categorized only iron and calcium as food components that are recommended for high-priority monitoring status because they represent public health problems in the population." "Ill effects of low maternal calcium intakes on the mother or fetus have not been reported. Nevertheless, there is some concern that low calcium intakes during pregnancy might impair bone mineral deposition, especially in women under age 25." "The subcommittee defined a low calcium intake to be less than 600 mg/day; below this level of intake the average U.S. adult develops a negative calcium balance. . . ." "A pregnant woman whose calcium intake is less than 600 mg/day . . . should be advised to increase her consumption of ... food sources of calcium or to take a calcium supplement at mealtimes that provides 600 mg of calcium per day." "The subcommittee does not recommend routine supplementation of pregnant women in the United States with calcium, magnesium, or vitamin D." "No adverse consequences of low calcium intake during pregnancy have been documented. . . . In the United States . . . there have been no reports on the effect of maternal calcium supplementation on bone mineralization of the mother or the fetus" (Institute of Medicine, 1990).

5. **Critical assumptions**

Although in general the documents are based mainly on evidence, inevitably some assumptions about various aspects of the calcium economy creep in, partly because certain of the data needed to provide a comprehensive picture were not available at the time the documents were compiled.
"If [in adolescents] obligatory calcium losses in urine, feces, and sweat are not greater than average, the calcium RDAs are adequate provided that 50 percent of the calcium ingested is absorbed" (National Research Council, 1989a).

"The quantity of dietary calcium required to achieve peak bone mass is greater than that required to replace obligatory losses of this ion in urine, feces, and sweat (approximately 200 to 300 mg/day)" (National Research Council, 1989a).

"The RDA for calcium is based upon an obligatory calcium loss of 200 to 250 mg/d" (National Research Council, 1989b) and absorption conservatively estimated to be 40 percent.

[Note: The recommended energy intake for adult females is 2200 kcal/d (National Research Council, 1989b). Estimates of the adequacy of intake of various nutrients might be based on the presumption that total food intake reached that level of intake. The report of the Committee on Diet and Health, on the other hand, recognizes both that energy intake is often substantially below RDA's recommendations, and that it is difficult to get sufficient intake of many nutrients at prevailing energy intakes (National Research Council, 1989a).]

6. Possible harm associated with overconsumption

Only two of the documents touch on possible problems of overconsumption of calcium. The principal concern is nephrolithiasis. However, as the scant attention given the topic suggests, even this complication is not considered a major problem.

"Although no adverse effects have been observed in many healthy adults consuming up to 2,500 mg of calcium per day, high intakes may induce constipation and place up to half of otherwise healthy hypercalciuric males at increased risk of urinary stone formation. A high calcium intake may inhibit the intestinal absorption of iron, zinc, and other essential minerals. ... Ingestion of very large amounts may result in hypercalciuria, hypercalcemia, and deterioration in renal function in both sexes. ... Supplementation to a total calcium intake much above the RDA is not recommended" (National Research Council, 1989b).

"Excessive calcium intake can cause inappropriate mineralization, particularly in the soft tissues, ...[some people] who have a defective intestinal barrier to calcium may absorb too much calcium ... women who are at high risk for development of renal stones [should be] screened for excessive urinary concentrations of calcium to determine the appropriate dose" (U.S. Department of Health and Human Services, 1988).

7. Comment

Throughout these documents there is recognition that calcium intake is important to insure full achievement of the genetic potential for adult bone mass (peak bone mass). There is little or no apparent disagreement concerning that point and not much about the quantity of calcium required during growth. The RDA has been at 1200 mg (30 mmol) during adolescence for many years, and that intake level was extended through age 24 in the most recent edition (National Research Council, 1989b), in recognition of recent evidence that skeletal consolidation continues for several years after linear growth has ceased. There is a near universal agreement that achieving the highest peak bone mass possible within one's genetic program is perhaps the best available protection against late-life fractures due to the inevitable bone loss of aging.
The documents also express a predominant view that an adequate calcium intake remains important in mature adults, though here ambivalence within several of the documents and contradictions between them become evident. For example, the report of the Committee on Diet and Health states "There is strong evidence ... that calcium supplementation has a modest influence on preventing cortical bone loss" and that "... low calcium intake is associated with a higher frequency of fractures ..." At the same time, it concludes "... the potential benefits of calcium intakes above the RDAs to prevent osteoporosis ... are not well documented and do not justify the use of calcium supplements."

Only three documents directly address calcium needs during pregnancy and lactation. The National Research Council (1989b) is firm about the need for 30 mmol/day during pregnancy in women of all ages, while the report on "Nutrition During Pregnancy" (Institute of Medicine, 1990) is concerned only to insure intakes of 15 mmol/day — a nontrivial difference. The calcium-related nutrition objective of "Healthy People 2000" for adolescents and pregnant women calls for three or more servings daily of foods rich in calcium (which the document typifies as a serving of dairy products) (U.S. Department of Health and Human Services, 1991). This translates, when combined with calcium in other foods, to an intake in the range of 27.5 to 32.5 mmol/day, and is thus consistent with the recommendation of the National Research Council (1989b), if not that of the Institute of Medicine (1990). The same "Healthy People 2000" objective calls for at least 2 servings daily for all other adults, which, with the calcium in other foods, translates to about 20 mmol/day, also quite consistent with the 1989 RDA.

The documents most specifically concerned with the problem of osteoporosis all recognize the existence of a special problem during later adult years and generally call for higher daily intakes, especially in women, than do the documents concerned mainly with general nutrition. Recommended intakes are typically 25 to 37.5 mmol/day during that period (Consensus Conference, 1984; U.S. Department of Health and Human Services, 1986; Food and Drug Administration, 1989). In coming to this higher intake recommendation, these documents acknowledged the fact that there is some disagreement in the scientific community about the need for such intakes, but concluded that both the weight of the evidence and prudent considerations support the higher recommendation.

Since replacement of obligatory loss is the principal reason for continuing calcium requirement in mature adults, assumptions concerning the magnitude of that loss, as well as concerning intestinal absorption efficiency, are critical for estimation of intake requirements. Where mentioned at all, the benchmark documents agree upon a figure of obligatory excretory loss in the range of 5 to 7.5 mmol/day. This figure is supported both by the evidence available at the time, as well as by subsequent reports (e.g., Hasling et al., 1990). However, the studies that provide the basis for this value were performed mainly in white women consuming typical Western diets (which are often relatively high in protein and sodium, both of which increase urinary calcium losses). There is evidence that U.S. blacks have lower levels of obligatory loss (Bell et al., 1985a,b), and scant data are available for obligatory loss in Hispanic or oriental populations.

Absorption efficiency is assumed to be at least 50 percent in adolescents (National Research Council, 1989a) and 40 percent in adults (National Research Council, 1989b). At the time of the compilation of these documents, no direct measurements of absorption in adolescents were available; however, there was a substantial body of evidence indicating that adult absorption efficiency is substantially below the 40 percent figure used by RDA (e.g., Heaney et al., 1975; Recker et al., 1988). Subsequent studies have confirmed and extended these data (e.g., Dawson-Hughes et al., 1988; Eastell et al., 1989; Hasling et al., 1990; Heaney, 1989; Heaney and Recker, 1986; Heaney et al., 1989a; Shipp et al., 1987). The RDA assumed value for absorption fraction is thus, on the evidence, substantially too high. New data (e.g., Miller et al., 1988) show that absorption fraction in adolescents is very little different from adults and is almost certainly well below the assumed 50 percent value.
Finally, the benchmark documents, as a group, tend to blur the distinction between high calcium intakes from food sources and from supplements, an important difference. Only one deals specifically with the problem of poor availability of many supplement formulations (Food and Drug Administration, 1989).

B. EVIDENCE NOT CONSIDERED IN THE BENCHMARK DOCUMENTS

Both because some of the benchmark documents do not explicitly list all their background source materials and because one cannot be certain how those listed were used, it is not possible to address completely the question of whether those documents may have failed to consider certain bodies of evidence. However, as already noted, the RDA assumption concerning adult absorptive performance seems to have ignored studies from several sources pointing to a lower figure than the one used. Additionally, two broad areas that have relevance to this question may not have been adequately addressed. These are: a) insights from comparative nutrition; and b) the secular changes in both total nutrient intake and in nutrient composition of American diets which have occurred over the past 50 years.

1. Insights from comparative nutrition

Most mammals, irrespective of the character of their digestive systems, have diets with much higher calcium nutrient densities than do contemporary Western humans and, after adjusting for body size, absolute calcium intakes that are higher still. This is the best indication available concerning the levels of dietary calcium to which our evolving absorptive system would have adapted. The chimpanzee, for example, ingests a diet with a calcium density of c. 2 to 2.5 mmol/100 kcal (Eaton and Konner, 1985; Eaton and Nelson, 1991). Contemporary hunter–gatherers (e.g., bushmen) eat foods with an average calcium density nearly the same (c. 1.75 to 2.25 mmol/100 kcal) (Eaton and Konner, 1985). By contrast, the median calcium density in NHANES II was c. 0.75 for adult women, only one-third the level found in the diets of either our closest primate relatives or contemporary humans considered to typify preagricultural Homo sapiens. Today, because of relatively lower energy expenditures, total calcium intakes of Western adults are even lower relative to high primates or hunter–gatherers than the nutrient density disparity would suggest.

Contemporary requirements cannot validly be estimated from such data. However, awareness of the fact that the primitive and proto–human calcium intake was substantially higher than our own helps to shape the context in which nutritionists may ponder both requirements and the production of harmful effects from intakes which seem large when compared with contemporary practice.

2. Secular change in nutrient intake

While detailed national tracking of nutrient intake began only 20 years ago, with NHANES I, there are scattered data from the period immediately after World War II, as well as a general recognition of decreased energy expenditure over the past half century (with a corresponding decrease in energy intake as well). In 1948 a study in Groton Township, New York, found that women of child–bearing age consumed about 2000 kcal/day (Young and Pilcher, 1950). The Four Cities Study, also conducted in 1948 (Clark and Fincher, 1954), found energy intake of women aged 30–49 to be c. 1800 kcal/d. By contrast, the most recent Continuing Survey of Food Intake of Individuals (CSFII 1986) found median energy intake for women in the same age range to be about 1400 kcal/d, or approximately 25 percent lower than 40 years earlier (U.S. Department of Agriculture, 1988). The report of the Committee on
Diet and Health explicitly acknowledges this change and points to the difficulty it may create in getting adequate quantities of nutrients (National Research Council, 1989a).

Ignoring entirely any qualitative changes in the types of food ingested, this secular drop in total food intake tends to carry with it a decline in intake of minerals and trace nutrients. In any case, it undermines the assumption, in RDA, of an energy intake of 2200 kcal/day.
II. CRITERIA FOR SELECTION OF STUDIES INCLUDED IN THE APPENDIX

All articles from indexed journals related to the topic of this review, as well as several symposium volumes and monographs, were evaluated for inclusion in the Appendix. Abstracts from current scientific meetings were also included if the author reviewed the manuscript itself. Selection criteria were as follows:

- **Date:** Generally 1987 or thereafter. A few 1986 studies were included if they seemed to have special relevance to certain of the issues specified for inclusion in this review (e.g., Kapsner et al., 1986), or if it could not be determined whether the papers concerned had been specifically included in the background of the benchmark documents, or if comparable work had not been published after 1987.

- **Content:** With few exceptions, for a study to have been included, calcium intake must have been controlled or measured. Correspondingly, there had to have been some measure of bone status, either direct (e.g., bone mineral content) or indirect (e.g., calcium balance or its components). This restriction is responsive to the context of this review, which is not about calcium metabolism but about the relationship between calcium intake and bone health (specifically the prevention of the condition, osteoporosis).

- **Population:** Only one animal study was included. The benchmark documents specifically recognized the relationship in animals between calcium intake and bone mass/bone loss, a field in which there is a consistent body of experimental evidence extending back at least to 1928. Thus, the relationship is not in question. The issue that remained was whether the relationship holds in humans in the range of intakes likely to be ingested and, if so, what might be the intake level. Both are questions animal studies cannot answer. The one animal study that is included was selected because it addressed the important matter of nutritional repair of an early-life calcium deficiency.

Several re-analyses of previously published data are cited in the text but not included in the Appendix. Similarly, many letters, editorial comments, and reviews have been published since 1987, but none contained new data, and so these, too, were not included in the Appendix. The only exception is the meta-analysis of Cumming (1990) which was directly responsive to the purpose of this review. Many other references, not included in the Appendix, are cited in the text of the review insofar as they provide documentation for statements contained therein. No date restrictions were applied to these citations.
III. RESULTS OF HUMAN STUDIES OF A CALCIUM–OSTEOPOROSIS RELATIONSHIP

A. PHYSIOLOGICAL ROLE AND NORMAL METABOLISM OF CALCIUM

Calcium plays two distinct roles in mammalian physiology. One, systemic, is as a metal co-factor for a large number of catalytic and structural proteins, both intra- and extracellular. The other, skeletal, is as a bulk mineral component of bone.

1. Systemic role

Within cells, calcium is a nearly universal second messenger mediating such diverse responses as muscle contraction, mitosis, and secretion. Extracellularly, it is important for blood coagulation and neuromuscular signal transmission. The cells themselves regulate the concentration of free calcium ion in their cytosol, keeping it at least three orders of magnitude lower than in the surrounding extracellular fluid (ECF). They do this both by pumping calcium up a concentration gradient out to the ECF and by sequestering calcium in intracellular vesicles, such as the sarcoplasmic reticulum in muscle. ECF \([\text{Ca}^{++}]\) concentration is tightly regulated around a value of about 1.2 mM, mainly through parathyroid hormone (PTH), calcitonin, and calcitriol. The secretion of all three is responsive directly or indirectly to changes in ECF \([\text{Ca}^{++}]\) levels.

Calcium enters the body solely through the mouth, principally as a food component, but to a limited extent through drinking water (if water sources are hard), the latter either drunk as such or in beverages made from water. Absorption from ingested food or drink occurs by both active transport across the intestinal mucosa and by passive diffusion from the gut lumen into the blood. Absorption occurs in all regions of the intestine from the duodenum through the cecum, but is most efficient in the duodenum and least in the colon. Absorption efficiency rises as intake drops, partly because of increased active transport evoked by calcitriol and partly because transport capacity is limited. (In the short time from entry into the duodenum to exit from the ileum, a smaller fraction of a large load can be transported than of a small.)

Absorption efficiency for calcium is relatively poor in comparison with the monovalent cations, averaging from 25 to 30 percent in healthy adult women ingesting intakes in the range of the RDA (Heaney and Recker, 1986; Heaney et al., 1989a). This value for efficiency applies to the fraction of ingested food calcium transported from the intestinal lumen into the blood and is larger than the nutritionally relevant measure, net absorption, which is given by the difference between ingested intake and fecal output. The two absorption measures differ because calcium enters the gut lumen both with the digestive juices and in sloughed off mucosal cells (which turn over about every five days and, if like other soft tissue cells, contain about 0.125 mmol Ca/100 g wet weight). The total calcium from these endogenous sources averages roughly 3.5 to 3.75 mmol/day in adult women (Heaney and Skillman, 1964). It is subject to the same inefficient absorptive process as is ingested calcium, and hence is largely lost into the feces. Simple calculation suffices to show that, at an intake equal to the adult RDA, and with, for example, a 25 percent overall absorption efficiency, absorbed calcium is only 2.0 to 2.25 mmol and thus net absorption amounts to only about 11 to 12 percent of intake, i.e., less than half of total absorption. At low absorption efficiencies, the addition of this endogenous calcium to the fecal stream causes fecal calcium to exceed ingested intake, and net absorption is thus negative.

Net absorption needs, of course, to be positive during growth, pregnancy, and lactation, because the skeletal mass of the child, of the fetus, or of the suckling infant needs the calcium for its own growth.
But net absorption must be positive also in mature adults, who are not pregnant or lactating, in order to offset obligatory losses, which occur principally through the kidney and the skin. (Digestive juice losses are directly factored into the calculation of net absorption.) Dermal losses consist of sweat, hair, nails, and desquamated skin cells, all of which contain small amounts of calcium. In toto, dermal losses are usually estimated to be in the range of 0.4 to 0.5 mmol/day, but Jensen et al. (1983), comparing whole body tracer retention with excreted tracer, have recently calculated dermal losses to be as high as 1.5 mmol/day in mature, non-exercising adults.

Dermal losses are elevated in hyperparathyroidism (Charles, 1989), possibly reflecting the hypercalcemia found in these patients, but are not known to be controllable by the hormones which regulate the calcium economy. Intestinal losses also are not influenced by the calcium-regulating hormones, and hence both remain relatively constant even in the face of calcium deficiency. Urinary calcium, by contrast, is directly adjusted by calcium-conserving homeostatic stimuli (principally parathyroid hormone secretion) to help maintain plasma calcium levels. Under certain experimental or clinical conditions, urinary calcium losses can be reduced to very low levels. However, this type of conservation is either very limited or absent entirely, both in normal adult Caucasian women and in adolescents. In adolescents, urine calcium typically remains above 2.5 mmol/d on intakes as low as 5 mmol/d (Matkovic, 1991; Matkovic et al., 1990). This is a figure very close to the value reported by Lemann et al. (1979) for normal adults of both sexes studied at comparable intakes, but for whom there is no growth requirement. For adult women, both Heaney (personal communication) and Nordin et al. (1987) report urine calcium values about 2 mmol/d on intakes at which net absorption is zero.

Individuals with idiopathic hypercalciuria are even less able to conserve calcium at the kidney. In at least two reports (Fuss et al., 1990a,b) male stone formers (whose numbers include many hypercalci-uric individuals) have been found to have significantly reduced bone density. Coe et al. (1988) studied patients with idiopathic hypercalciuria defined as a 24-hour urine calcium > 8.75 mmol. They found them generally to be in negative calcium balance. However, when treated with thiazides for 3 months these individuals invariably exhibited both reduced urine calcium loss and improved calcium balance, the latter by an average of about 2.2 mmol/d, a biologically important change.

Some authors have argued (e.g., Kanis and Passmore, 1989a,b) that failure to reduce urinary calcium losses under such circumstances is evidence of calcium sufficiency, and while that might conceivably be true in adults, it certainly cannot be so in adolescents, whose skeletal growth needs require positive balance in excess of 5 mmol/day. As Matkovic et al. (1990) showed, adolescent females continue to excrete relatively large amounts of calcium in the urine even when their diets are so restricted as to preclude any calcium retention at all.

The full explanation for this seemingly anomalous behavior is unknown. Some of it may possibly reflect an evolutionary absence of exposure to prolonged low calcium intake. Some of it is most probably due to prevailing levels of protein intake, since urine calcium losses with total parenteral nutrition are mainly controlled by the protein/amino acid content of the infusate, rather than by its calcium content (Wood et al., 1984). High sodium intakes are also known to elevate urinary calcium excretion (Nordin and Polley, 1987). There may well be other factors contributing to the relatively high obligatory losses noted in adult women and adolescents but, whatever the causes, the net result is a limitation in the ability of the kidney to reduce urinary calcium losses in response to calcium-conserving hormonal stimuli. American blacks have lower levels of urinary loss and better absorption efficiency for the same levels of food intake (Bell et al., 1985a,b), and thus there may be a racial basis for differences in calcium requirements.
2. **Skeletal role**

The second physiological role of calcium resides in its position as the principal cation of bone mineral, comprising nearly 40 percent of the ash content of bone and roughly 20 percent of its wet weight. Bone mineral is a complex mixture of phosphate and carbonate salts of calcium, frequently termed simply hydroxyapatite (which is an oversimplification). The extracellular material of bone makes up about 95 percent of its volume and consists mainly of a composite of mineral crystals encrusting an ordered array of long protein fiber bundles (mainly collagen). The mineral phase is essential for the stiffness and hardiness of bone, and thus for the mechanical integrity and structural utility of bone.

Bone is formed by osteoblasts, which first deposit the protein matrix, then act on it to create crystal nuclei for calcium phosphate. Thereafter, these nuclei grow by accretion, without further cell work, spontaneously adding calcium and phosphate ions drawn out of the blood flowing past the mineralizing site. This process creates one of the calcium drains to which the system regulating blood calcium must continuously respond.

Once deposited, calcium is permanently trapped in bone and cannot be removed except by the process of bone resorption, in which osteoclasts attach to a bony surface, secrete acid and proteolytic enzymes, and thereby physically remove a volume of bone, both its mineral and its matrix. The calcium content of that volume is released into the circulating fluid and becomes available both to meet the calcium demands of other bony sites that happen currently to be in their mineralization phase and to support the ECF [Ca$^{++}$] against the drain of obligatory losses.

Collectively these processes of formation and resorption are termed bone "turnover" or "remodeling." Remodeling fluxes into and out of bone are, in the mature adult, typically in the range of 7 to 12 mmol/day, or about 1.5 to 2.0 times as large as the aggregate of the external fluxes consisting of absorption and excretion. While resorption and formation are necessarily separated temporally at any given bony site, they are relatively tightly coupled to one another across the entire skeleton, by both systemic and local factors. This coupling means that, at a total skeletal level, if formation is high, resorption will be high as well (and vice versa). However, the two processes are rarely exactly equal in magnitude. During the third decade of life, for example, formation exceeds resorption and thus bone mass continues to increase even though linear growth has ceased. The same kind of imbalance results in the increase in bone mass following increased mechanical loading. Conversely, with physical inactivity, resorption exceeds formation, and bone mass decreases. The benchmark documents recognize a further nutritional cause of remodeling imbalance, namely external (dietary) calcium deficiency (Consensus Conference, 1984; National Research Council, 1989a); in this case a resorptive excess sustains ECF [Ca$^{++}$] levels in lieu of calcium made available through the diet.

B. **Basis of Association of Calcium with Osteoporosis**

The basis for the association between calcium intake and bone health has already been set forth in a general way in the foregoing discussion of calcium metabolism, and can be succinctly summarized as follows: if absorption of calcium from food sources is not sufficient to offset obligatory losses (i.e., the body is in negative calcium balance), then the resorptive component of bone remodeling exceeds the amount of new bone formed and the imbalance results in a loss of bone mass. This basis is recognized in the benchmark documents including the Consensus Conference (1984), the U.S. Department of Health and Human Services (1986), and the National Research Council (1989a). Absolutely low intakes are only one of the reasons for negative balance. Others include poor absorption efficiency from otherwise adequate diets and excessive obligatory losses. Both problems are relatively common in the U.S. Caucasian population. [See, for example, the lower two-thirds of the range of absorption efficiencies cited in Heaney et al. (1989a) and the data on urinary calcium loss]
in adolescents presented by Matkovic et al. (1990)]. Such differences in absorption and excretion contribute importantly to differences in requirement and help to explain the sometimes low correlations found between intake itself and various bone status indicators.

The body's ability to adjust bone remodeling balance is an important physiological defense of the ECF calcium level, providing needed calcium when the level would otherwise drop and soaking up surplus calcium when it would otherwise rise. However, in view of the calcium abundance in the diets of virtually all mammals, this mechanism for providing needed calcium in subhuman species functions mainly during periods of excessive skeletal demand or transient environmental scarcity. This is illustrated most clearly in what happens during annual antler formation in several species of deer (Banks et al., 1968). Antlers consist of bone; their growth is usually so rapid that absorbed food calcium cannot keep up with demand, particularly given the relatively poor nutritional quality of early spring food sources. Accordingly, PTH secretion increases sharply when antler formation begins, and a burst of bone remodeling is initiated throughout the skeleton. Since the first phase of remodeling is resorptive, a temporary surplus of calcium is made available for antler mineralization. Later, antler growth slows or stops and the remodeling loci throughout the skeleton enter their own phase of bone formation (which proceeds at a somewhat slower pace than for the antlers). Those sites then get the calcium they need from calcium-rich summer grasses and leaves. Averaged over the year, environmental calcium is quite sufficient to permit deer to build and to discard all that accumulated antler calcium each year, and then to start the process all over again. Remodeling is adjusted in this case to help with a temporary calcium "cash-flow" problem.

So long as the microscopic scaffolding of bone remains intact, as in the deer, there is always the potential for restoration of most or all of the bone lost through remodeling imbalances, at least if adequate exogenous calcium again becomes available. This borrowing mechanism creates a problem when absorbed dietary calcium remains chronically below the level of daily demands or losses. Since the calcium borrowed from bone cannot be repaid under those circumstances, the remodeling imbalance continues and bone mass gradually declines. If this process continues to the point where structural elements are lost (e.g., trabecular plates are perforated or trabecular spicules disconnected), much or all of the lost bone can no longer be replaced; at least it cannot be reversed by replacement of the missing nutrient.

The significance of diet-related bone loss for bone health and disease lies in the fact that bone mass is a major determinant of the strength of the skeleton. It is not the only determinant; failure to repair accumulated fatigue damage and the development of trabecular disconnection both directly affect the material properties of the structure, independently of mass, but these factors bear no known relationship to calcium intake and will not be further discussed in what follows. Mass loss is generally considered a necessary condition for low trauma fractures, and for many years it was treated as virtually synonymous with the diagnosis "osteoporosis". Hence, the focus of calcium as a nutrient related to osteoporosis lies in its importance both for achieving genetically programmed bone mass during about the first 30 to 35 years of life and in maintaining that bone during the remaining years of life.

A distinct case, perhaps more appropriately classed as therapeutic nutrition, arises whenever an individual recovers from a prolonged period of reduced physical activity (whether from occupational change or from illness or injury). Bone mass is always lost when bones are unloaded, and if the lost bone is to be replaced during recovery, the diet must contain enough calcium not only to offset current obligatory losses but to support restoration of optimal bone mass. LeBlanc et al. (1990), building on a large number of earlier NASA-sponsored immobilization studies, showed convincingly that there was substantial bone lost from several regions of the spine and lower extremities during bedrest. During reambulation calcaneal bone mineral density returned to normal, but other sites were slow to do so.
Inadequate calcium intake may be a partial explanation. The calcium needs of bone rebuilding following illness or injury are not addressed in any of the benchmark documents, even though some (e.g., U.S. Department of Health and Human Services, 1988) do address the needs of subclasses of the population.

C. LEVELS OF CALCIUM INTAKE REQUIRED FOR BONE HEALTH AND EVALUATION OF THE EVIDENCE

There is general acceptance by the scientific community of the foregoing principles and mechanisms, and this provides the foundation for the recommendations contained in the benchmark documents. However, while there may be consensus on the basics of the relationship of calcium and bone, there is residual controversy surrounding the question of how much dietary calcium is enough to assure the twin goals of achieving genetically programmed bone mass and protecting adult mass. This section will both examine the evidence accumulated since 1987 that bears on this matter and will attempt, to the extent possible, to explore possible reasons for apparent discrepancies or disagreements.

1. Studies of the relationship of calcium intake to bone status

Calcium is a threshold nutrient (as, for example, is iron). Forbes et al. (1979) showed in growing rats that femur bone mass was a linear function of dietary calcium content up to values of about 0.6 percent. Above that level bone mass remained constant, irrespective of further increases in intake. Linear growth was not limited in these animals at subthreshold levels of calcium intake, but bone mass was. Current models of bone metabolism would explain this effect by a relative resorptive excess on the sub-threshold diets, resulting in a tearing down of some of the bone deposited during growth so that its calcium could support the demands of linear growth. The resulting bone is thus of normal external size, but of increased internal porosity and decreased cortical thickness. There is no evidence to suggest that dietary calcium itself affects the mineralization process so long as serum calcium levels are maintained, either during growth or later, although some data suggest that low calcium intakes may limit linear growth. This may occur in some growing animal models with very low calcium intakes, and has been reported for Scottish school children (Leighton and McKinlay, 1980), in whom addition of 12 ounces of milk per day to the diet of one group resulted in substantially greater linear growth. But it is not possible, in such experiments, to tease apart the effects due specifically to calcium from the effects of the associated extra protein and energy. In general, it seems probable that the effect of low calcium intake on the growing skeleton is mediated largely through resorptive modulation of the balance between bone formation and bone resorption.

In thinking about the requirement for humans, it is important to be clear that while sufficient exogenous calcium must be present to support growth and to maintain skeletal mass, additional calcium above the threshold (whatever may be its value) will not produce more bone than is required either by the genetic program or by current levels of mechanical loading. The notion of a requirement is thus tied to this threshold. An individual's requirement is the inflection point of the curve relating bone mass to intake, i.e., the threshold, and an RDA is the corresponding point for a population. In both, further increases in intake produce no additional benefit or confer no additional protection. The following discussion will therefore center around whether the available evidence in humans supports the conclusion that variations in calcium intake in the existing range of human diets have an important effect on bone mass.
Does the available evidence in humans support the conclusion that variations in calcium intake in the existing range of human diets have an important effect on bone mass?

Cumming (1990) conducted a meta-analysis of published studies up through roughly the time of the benchmark documents and concluded that the clear weight of evidence indicated that higher calcium intakes, up through and including the intakes associated with calcium supplementation, had a beneficial effect on bone mass in postmenopausal women. Since publication of the studies included in the meta-analysis, a surprisingly large number of additional reports on this topic have been published (see Appendix). Criteria used for selection of published reports for this evaluation are described above. These reports include at least six randomized controlled trials (RCT) designed specifically to evaluate the role of calcium (Andon et al., 1991a; Baran et al., 1989; Dawson-Hughes et al., 1990; Elders et al., 1991; Prince et al., 1991; Smith et al., 1991). Five were in peri- or postmenopausal, and one in premenopausal, women. All showed that higher calcium intakes reduced or eliminated bone loss relative to placebo-treated controls. The study of Dawson-Hughes et al. (1990) is probably the strongest, both because of its size and because of the additional light it sheds on the confounding problem of estrogen withdrawal bone loss in the immediate postmenopause (see below).

Additionally, there have been about 18 distinct observational studies (see Appendix) testing the relationship between estimated calcium intake and bone mass at one or more sites. These studies involved over 2,500 individuals, almost all of them Caucasian women. Ten of the 18 studies reported a statistically significant positive association between calcium intake and bone mass at one or more sites, a proportion similar to what was found for papers published up to the time of the benchmark documents (see, e.g., Heaney, 1986; Food and Drug Administration, 1989).

Four epidemiologic studies of the relationship of calcium intake in hip fractures have been published since 1988, three as cohort studies, and one using a case-control design. The three cohort design studies reported a reduced risk of fracture at high calcium intakes, two of them for both men and women, and one for men only. The case-control study found no protective effect of high calcium intake for either sex.

Two additional avenues of approach to this problem are reflected in RCTs describing effects of calcitriol in patients with osteoporosis (Gallagher and Goldgar, 1990; Gallagher and Riggs, 1990) and in various studies of the relationship of thiazide use to skeletal health (Coe et al., 1988; LaCroix et al., 1990; Ray et al., 1989). The two calcitriol studies both found significantly improved bone mass and/or more positive calcium balance in patients given relatively modest doses of calcitriol, a benefit plausibly due to improved calcium absorption in the treated subjects. The fact that the calcium absorbed under the influence of calcitriol was not simply re-excreted in the urine is presumptive evidence that these individuals had a capacity to reduce bone loss and/or improve bone mass, which, in the untreated state, was limited by calcium availability from the diet.

The studies of thiazide use approach the problem from the other side, that is, excessive urinary calcium loss. These studies found a reduced hip fracture risk associated with thiazide use, one of them with a clear exposure-related gradient (Ray et al., 1989). The studies were controlled for various confounding variables. Ray et al. (1989) evaluated also the possibility of an association between bone mass and hypertension itself (the context in which thiazide use would likely be employed) and found the effect to be specific for thiazides. The authors of these studies considered that it was the recognized calcium-sparing effect of thiazides that was responsible for the reduced hip fracture risk in thiazide users in these studies. The possibility of a direct effect of thiazides on bone resorption cannot be completely excluded. Lemann et al. (1986) drew that conclusion from a study in which they experimentally elevated serum calcitriol levels and yet found suppression of urinary hydroxyproline excretion when thiazides were given. However, their data are equally well explained by suppression
of endogenous PTH release produced by the combined effects of calcitriol–induced elevation in calcium absorption and thiazide–induced reduction in calcium excretory loss. Since they measured PTH levels only in the fasting state, they were unable to evaluate this alternative explanation.

The findings in other special situations shed additional light on this topic. Fuss et al. (1990a,b) found reduced forearm bone mass in male idiopathic renal stone formers, presumably due in part to the inclusion of some (possibly many) individuals with excessive urinary calcium losses in any such group of men. These investigators also showed that restricted calcium intakes in such patients were associated with further reduction in bone mass.

Studies of both the thiazide users and the stone formers highlight the probable role of urinary calcium loss in the pathogenesis of low bone mass and hence of skeletal fragility.

Other special situations are more difficult to interpret. Bone mass is clearly low in anorexia nervosa (e.g., Bachrach et al., 1990), but this is a complex state with multiple nutritional and endocrine deficiencies, and the low bone mass of these individuals is almost certainly not due solely to their typically low calcium intakes. Similarly, there is a tendency for bone to be lost during lactation (e.g., Byrne et al., 1987; Chan et al., 1987). Probably some of this can be reduced by ensuring an adequate intake of calcium, particularly in adolescents. But once again, lactation is a period of complicated endocrine change, and it seems implausible that calcium intake alone is responsible for the bone status of these women.

Several recently published studies evaluated the interaction of exercise and calcium intake (e.g., Chow et al., 1987; Halioua and Anderson, 1989; Kanders et al., 1988). In general, where found, the effect is a positive one. This is a nontrivial issue, because if increased loading is to lead to an increase in bone mass, there must be a supply of calcium.

In the one animal study included in the Appendix, Thomas et al. (1991) reared rats on calcium–deprived rations and then attempted repletion at about the time of sexual maturity. A considerable increase in bone mass resulted, even though linear growth had slowed. This study may have relevance to the problem commonly encountered among young women, whose intake of calcium typically falls at or before puberty, but who, in their twenties, become more nutritionally conscious. To the extent that these data in rats can be extended to humans, these young women may have some potential for late achievement of genetically programmed peak mass.

2. Possible explanations for investigational discrepancies

Insofar as can be judged from published reviews and editorials, there would appear to be a majority view among investigators in the nutritional community that calcium intake within the range of plausible diets and supplementation has a positive influence on bone status (e.g., Arnaud and Sanchez, 1990; Barrett–Connor, 1989; Marcus, 1987; Nordin and Heaney, 1990a,b). There have, of course, been dissenting views (e.g., Kanis and Passmore, 1989a,b), which in turn have evoked a spate of correspondence in the respective medical journals. While it is never possible to say with certainty why two groups of scientists disagree, one can explore why, given the hypothesis of an important role of calcium intake in bone health, that role might not be apparent in various clinical investigations. Six such reasons can be cited:

- Multifactorial character of age–related change in bone mass and of bone fragility;
- Differing calcium intake distributions in various study populations;
• Inability in most types of studies to address the several causes of calcium deficiency, i.e.,
calcium deficiency may be due to low intake, but also to decreased absorptive performance or
to high obligatory excretory loss;

• Failure, in most studies of the postmenopausal period, to recognize the special circumstances
created by estrogen withdrawal in the few years immediately following hormone loss and, in
the analysis of published reports, to separate studies on the basis of proximity to menopause;

• Use of weak or inaccurate tools for estimating calcium intake in all studies except for inter-
vention or metabolic studies, and the seeming failure to recognize this limitation; and

• Insufficient power to detect plausible population-level correlations, if they exist, in many
published studies.

Because of the residue of disagreement among investigators in this field, these issues will be explored
briefly, not so much to demand the position of one side or the other, but to elucidate the several reasons
why studies may produce inconclusive or seemingly disparate findings.

a. Multifactorial character of change in bone mass and of bone fragility

Calcium, to the extent that it plays a role in bone health, is only one of many interacting factors.
Some of these factors remain unknown, or at least inadequately explored; hence, it is difficult to
control for them. Exercise, hormonal status, heredity, co-morbidity, medications, smoking, and alcohol
consumption are some of the major factors influencing bone mass and bone loss, in addition to
nutritional variables. These are all recognized in a general way, but are seldom adequately quantified
in observational studies. Further, trace metals, as the study of Smith et al. (1991) shows, may be yet
another confounding variable. It is likely that still others will be found. Finally, bone fragility, which
is the cause of low-trauma fractures, is probably due only partly to reduced bone mass. (See Chapter
I. B.) While the non-mass fragility factors may yet prove to have nutritional correlates, none is known
to date. Calcium deficiency, to the extent that it plays a role in this complex context, is postulated to
have an effect only on bone mass. Hence, the connection of calcium intake to fracture risk can be only
as good as the connection between bone mass and fracture.

b. Differing calcium intake distributions in various populations

Reported studies need to be interpreted against the national background of the individuals studied.
To the extent that low calcium intake contributes to the osteoporotic fracture problem, one would
expect to find the evidence most clearly presented in populations with intakes that span the range
from low to high, not in populations with predominantly high intakes. Beaton (1986) has discussed
this issue in detail. Thus, most of the reported studies from the Netherlands, where calcium intakes
are comparatively high, have shown little or no relationship between calcium intake and bone mass
(e.g., van Beresteijn et al., 1990a,b,c). The two studies of Elders et al. (1989, 1991) are comparative
exceptions for Dutch studies. In their cross-sectional investigation, Elders et al. (1989) found habitual
calcium intake to be a significant determinant of perimenopausal bone mass, but their data suggested
that calcium probably exerted its effect by influencing peak bone mass, rather than by influencing
menopausal bone loss. This conclusion is consistent with the findings in the study by Hansen et al.
(1991) in whose subjects high calcium intake was associated with higher bone density both before and
after menopause, but with no effect on the quantity of bone lost across menopause. In their
intervention study Elders et al. (1991), using daily supplements of 25 and 50 mmol of calcium in
addition to a basal diet averaging about 29 mmol/d, found a dose-related, step-wise reduction in rate
of bone loss before menopause, in the early postmenopause, and in the late postmenopause as well.
However, in these early postmenopausal women, mean rates of bone change were still negative, even
at the highest calcium intake (79 mmol/d), though less so than at lower intakes. These findings may reflect what some (e.g., Kanis and Passmore, 1989a,b) have termed a pharmacologic effect of calcium, i.e., a suppression of the basic remodeling process itself, which thereby slows change in bone mass irrespective of its cause.

In general, osteoporosis occurring in populations with high calcium intakes would be expected to have other causes than calcium deficiency, and one would not look to studies in such countries for evidence bearing on this question. Even the discrepancy between the hip fracture studies of Holbrook et al. (1988), who found a protective effect of high calcium intake, and of Wickham et al. (1989), who did not, may be due to differences in distribution of calcium intake between their respective populations. Mean calcium intake in the Wickham study was well into the upper tertile of intakes for the Holbrook study.

c. Inability in most studies to address the several bases for calcium deficiency

As already stressed, calcium deficiency may be caused not only by low intakes but also by inefficient absorption or by high obligatory losses, neither of which is quantified in most observational or even intervention studies. (For the most part, these causes of calcium deficiency can be satisfactorily measured only in metabolic studies.) The net result of ignoring these causes is a misclassification bias. Individuals classified as having high intakes may still actually be deficient if their absorptive or renal excretory performances are not appropriate for their intake. Conversely, other individuals with lower absolute intakes may be fully calcium replete if their absorptive and excretory processes have adapted sufficiently. If these misclassifications occur equally in both directions (which seems unlikely from the evidence available), the result would be only a loss of power (see below). But if the misclassification of deficient subjects as high-intake individuals predominates, the result will be a bias against finding a calcium effect.

d. Failure to recognize the special characteristics of the immediate postmenopausal period

It now seems increasingly clear that bone loss in the immediate postmenopausal period is due almost exclusively to loss of gonadal hormones. The same type of loss follows castration in males. While many of the details of the mechanism remain uncertain, it appears that this loss reflects a downward adjustment of bone mass to a new steady state, just as occurs with immobilization. During that approach to a new postmenopausal equilibrium value, nonhormonal forces, such as calcium or exercise, are relatively ineffective — largely because the change in bone mass is due specifically to absence of gonadal hormones and not to inadequate calcium intake or lack of exercise. In fact, during the few years after menopause, so much calcium may be made available from bone that there may be no external calcium requirement at all. However, when the new steady state is approached and bone loss slows, all the old interactions reappear.

This conceptual framework was not available to investigators until recently, which may explain why so many previous studies of calcium effect chose to address the early postmenopausal period. Those years are the time when bone loss is the most rapid and the value of successful intervention is most evident, so it is not surprising that it has been studied extensively. But loss at that life stage is best prevented by estrogen. This topic has been extensively explored elsewhere (Heaney, 1990). It is elucidated clearly in the recent study of Dawson-Hughes et al. (1990) in which, with the same investigational design, the same measurement methods, and the same calcium sources, a calcium supplement abolished age-related bone loss in women 6 or more years postmenopausal but was without effect in women within 1 to 5 years of menopause. This point is also illustrated by the study of Prince et al. (1991), who studied women over an average of 5 to 6 years postmenopause. Their subjects thus straddle the dividing line used by Dawson-Hughes et al. (1990) and would be predicted to exhibit only
a partial response to increased calcium intake. Prince et al. (1991), in fact, found a significant reduction in rate of loss in the calcium-supplemented group, but the effect was less than in a comparable estrogen-treated group, precisely as predicted for a group this close to menopause.

e. Use of weak and inaccurate instruments for assessing calcium intake

Most observational studies have assessed calcium intake at one, or rarely two points in time, using a food frequency questionnaire (FFQ) limited in some studies to as few as seven food items. Others used one-day recall, three-day diaries, and a few, seven-day diaries. Most have provided no validation for their method of estimating intakes, and where some validation was said to have been done, details were rarely given. This is a problem of under-appreciated importance. Only a few of the problems with assessing calcium intake by such tools can be addressed here.

Even when one knows to the milligram exactly what foods went into an individual's mouth, chemical analysis invariably reveals a somewhat different figure from what the food databases estimate for those same foods because of lot-to-lot variation in the nutrient content of foods. Charles (1989) found, under metabolic ward conditions, a correlation of only 0.87 between database values for calcium content of various diets and the actually analyzed contents. This means that fully one-fourth of the interindividual variation in intakes could not be explained by knowledge of the precise quantities of foods eaten. Correlations between food table and analyzed values also differ among laboratories. The problem is, understandably, even more difficult when one moves from subjects studied under metabolic ward conditions to a free-living population, where quantities consumed can only be estimated. Even seven-day diaries fall short of capturing adequately the full details of intake. (See Heaney et al., 1990a for a fuller discussion of this topic.) Given typical day-to-day variation in calcium intake, diaries extending as long as 13–15 days are often needed for an acceptably small error estimate.

FFQs, the most commonly used tool, are attractive for their simplicity and ease of administration, but are generally less accurate than multiple-day diaries. In several of the studies reported here, FFQs produced substantially higher intake estimates than did diet diaries taken at the same time in the same individuals. Bergman et al. (1990) reported that a FFQ produced more than 50 percent higher figures for some nutrients, notably calcium, than did a 3-day food record. Finally, FFQs are totally inadequate at the low end of the intake spectrum, since by design they include only relatively calcium-rich foods. Individuals whose intake is low, of course, do not often eat such foods, so FFQs fail entirely to capture whatever intake variability may exist among them.

The validation usually cited in published reports is to the effect that the FFQ value correlated with some other measure of calcium intake. Musgrave et al. (1989) reported a correlation coefficient of only 0.73 between a FFQ value for calcium intakes and a concurrently developed food record. But one would expect there to be some correlation. That is not the issue. What is at stake is substitution. How accurate is the substituted value? How faithfully does it capture the real value for which one is using it as a substitute? It is this chain of substitutions (FFQ for multiple-day food record; food record for actual quantities of foods consumed; data base values of foods consumed for actual food content) that degrades the estimate produced by the measures actually employed in most observational studies, whether cross-sectional or longitudinal.

A further problem is one-point sampling. Heaney et al. (1990a) have documented the quite considerable extent to which individual intakes vary over time. Only one study in the series reported here used multiple-point sampling (van Beresteyn et al., 1990b). Finally, there is the failure to include, in estimating intake, the calcium content of excipients in medications or supplements taken for some reason other than their (generally unrecognized) calcium content (Heaney et al.; 1990a). The error so introduced will generally be small, but in perhaps 5 to 10 percent of middle-aged or elderly
women it will result in a substantial misclassification bias, i.e., counting people as having low intakes when they are actually high. (See also Chapter III. H.)

What may be considered surprising in all this is the contrast between the great attention paid to the accuracy, sensitivity, and specificity of bone mass measurements and the concurrent use of inaccurate means to quantify what is postulated to be the independent variable in the hypothesis being tested. What should not be surprising, therefore, is that some of the reported studies failed to support the hypothesis.

f. Insufficient power

Power is a well–understood, if sometimes ignored, problem in studies testing an hypothesis. What has been little appreciated until recently is the relative magnitude of the calcium effect to be expected in observational studies in a free–living population, and the impact that that magnitude has on investigational power. For example, the longitudinal study of Riggs et al. (1987), interpreted by many investigators as showing no benefit from calcium, had a stated power to detect a population–level correlation in the range of 0.6 or higher. But even given zero errors in estimating either bone loss or calcium intake (which are not even remotely possible), the highest plausible population–level correlation has been estimated to be less than 0.4 (Avioli and Heaney, 1991). Given these problems with assessing calcium intake, it seems clear that the correlation likely to be detectable would have been less than 0.3 — far smaller than Riggs et al. (1987) could reliably have detected. This is a problem to which Cumming (1990) also referred in his meta-analysis.

3. Criteria for evaluation of evidence

In summarizing the data published on this topic since 1987, it is helpful to recognize that not all studies carry equal weight. To facilitate analysis, a useful way to categorize studies is by menopausal age of the subjects and by degree of investigator control over, and/or knowledge of, calcium intake. For reasons already discussed, studies in which calcium intake is not investigator–controlled are all biased toward the null hypothesis. When such studies find an effect, therefore, the result is more convincing than when they do not. In a similar way, as also discussed, endogenous calcium released from bone in the wake of gonadal hormone loss substitutes for, or displaces, exogenous calcium. For that reason, studies performed within the first five years after menopause should not be taken as evidence in regard to calcium requirement or calcium effect at other life stages. As shown in the 4–way breakdown presented in Table 2, the result of using these 2 criteria is to categorize the 41 relevant studies on Caucasian women contained in the Appendix.

For reasons just discussed, the most weight should be placed on studies in cell D of Table 2, i.e., those with controlled intakes and carried out in subjects either premenopausal or more than five years postmenopausal. Correspondingly, the least weight should be placed on studies in cell A, i.e., those in which neither condition is met. As Table 2 shows, of ten studies in cell D, all without exception found that calcium reduced or eliminated age–related bone loss or otherwise favorably influenced bone mass accumulation. By contrast, none of eight reports published since 1987 that fall into cell A, showed a positive effect of calcium intake on bone mass or bone loss. Similarly, only four of seven studies grouped in cell B, i.e., those which, despite having investigator–controlled calcium intake, included early postmenopausal women, showed a positive effect of calcium. This underscores the conclusion drawn earlier that calcium intake has less effect on bone mass or bone loss during the early years after menopause. Studies which concentrated on that life stage would be predicted to find no effect, and studies that mixed such women with others of different menopausal status would weaken their power to find an effect in those physiologically capable of responding. The importance of that early postmenopausal exclusion is clearly evident when one looks at the studies grouped in cell C, i.e.,

23
Table 2. Categorization of Studies, Drawn From the Appendix, of the Relation of Calcium Intake to Bone Status in Caucasian Women.¹,²

<table>
<thead>
<tr>
<th></th>
<th>NO</th>
<th>YES</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A 0/8</td>
<td>B 4/7</td>
<td>4/15</td>
</tr>
<tr>
<td>Women from 0 to 5 years postmenopausal excluded NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td>C 11/16</td>
<td>D 10/10</td>
<td>21/26</td>
</tr>
<tr>
<td>TOTAL</td>
<td>11/24</td>
<td>14/17</td>
<td>25/41</td>
</tr>
</tbody>
</table>

¹ Studies in which effects of other treatment agencies and/or physiologic status could not be separated from effects of calcium are not included in this summary table.

² The numerators of the fractions in the cells represent the number of positive studies in that category; the denominator represents the total number of studies, positive and negative.

³ "Investigator-controlled" includes both intervention trials and metabolic studies.
those that did exclude early postmenopausal women, but still had the bias toward the null hypothesis that goes along with inability of the investigator to control the calcium intake. Eleven of 16 studies in that group showed a significant calcium benefit.

Thus, while a majority of the studies included in Table 2 reported a benefit from calcium (25 of 41), this simple tallying of studies treats them all equally and does not do full justice to the data. What the analysis in Table 2 shows is that the proportion of positive studies rises with the rigor and salience of the scientific design. Twenty-one of 26 studies excluding early postmenopausal women were positive, as were 12 of 15 in which the investigators controlled the calcium intake. All 10 studies meeting both criteria showed a calcium benefit.

D. OPTIMAL LEVEL OF CONSUMPTION BEYOND WHICH NO BENEFIT WOULD BE EXPECTED

The bulk of the evidence, particularly for the better designed studies, supports the hypothesis that a higher calcium intake is more protective of bone than is a lower one. A question remains in respect to how much calcium is sufficient. In studies of Caucasians, intakes have generally varied over roughly an order of magnitude from c. 5 mmol/day to c. 50 mmol/day. None of the published studies was specifically designed to locate the threshold value above which one would expect (at a population level) no further benefit for further increases in intake. It must be said, therefore, that this value remains unknown, but that it probably varies at different life stages.

Dawson-Hughes et al. (1990) found a significant benefit when increasing intake for postmenopausal women from a mean of c. 10 to 12.5 mmol/day to c. 20 to 25 mmol, suggesting at least that the threshold is higher than the baseline dietary value of her subjects (which was not very different from the NHANES II median for women). Whether it would be higher than their supplemented value cannot be said. Bone loss in the supplemented patients was essentially zero over the two-year period of the study, and this might be interpreted to indicate that the threshold had been reached. However, there is always a transient remodeling when calcium intake is increased to a major extent, and this will interfere with ability to detect true rates of loss for at least the first several months after changing intake. Only rates of change during the second and subsequent years after a change in regimen can be used to deduce the new steady state. The report of Dawson-Hughes et al. (1990) does not provide sufficient information to be certain about that point; indeed the study was not designed to produce it.

That the threshold might be higher than the supplemented level reached in the Dawson-Hughes (1990) study is suggested by the data of Hansen et al. (1991), who noted that menopausal Danish women with intakes above 37.5 mmol/day had significantly higher bone mass than those with intakes below that level, and who found that, 12 years later, though having lost bone across menopause, the high intake women had completely retained their bone advantage relative to those with lower (but by U.S. standards, generous) intakes. Possibly pointing to the same conclusions is the study of Baran et al. (1989), in which premenopausal women with calcium intakes estimated at 22.5 mmol/day were losing bone at about 1 percent per year, whereas women supplemented to c. 37.5 mmol/day were not. However, the finding in this study of premenopausal loss is not a universal one and raises questions about the methods. Mazess and Barden (1991) found no bone loss whatsoever in longitudinal studies of premenopausal women, a finding which is confirmed by Recker et al. (1991).

One major metabolic study has been reported since the benchmark documents were published. Hasling et al. (1990) found that the mean calcium intake required to achieve zero balance in 85 women with osteoporosis was in the range of 34 to 35 mmol/day. This is virtually the same value as previously reported by Heaney et al. (1978) and summarized in one of the benchmark documents (Food and Drug
Administration, 1989). This independent confirmation of the balance values on which the original NIH Consensus Conference recommendations were based (Consensus Conference, 1984) constitutes further evidence that the threshold in postmenopausal women might be higher than the current RDA published by the National Research Council (1989b).

Matkovic (1991) has recently assembled all the published balance studies on growing children and young adults, a total of 487 individual balances in all. These data contain potentially useful information about the location of the intake threshold during growth. He found that, at all ages, there was a strong positive correlation between intake and balance for the lower quartile of intakes, and no significant correlation for the upper quartile. This finding, consistent across all four age groups, confirms the threshold behavior of calcium intake in these growing children. It is also, incidentally, a refutation of the charge by Kanis and Passmore (1989a,b) that the correlation between intake and balance is spurious and artificial. If it were as these investigators have alleged, there is no reason why a correlation would not occur at the higher intakes as well as at the lower. An approach to estimating the inflection point in these sets of data (Matkovic and Heaney, 1991) suggests that the threshold during adolescence is c. 35 to 40 mmol/day, and during the years from 18 to 30, c. 25 to 27.5 mmol/day. The first value is about 20 to 25 percent higher than the current RDA, and the second very close to the current RDA.

Supporting the conclusion that the requirement during adolescence is at least as high as this estimate suggests is the finding by Matkovic et al. (1990) that even large increases in calcium intake have only trivial effects on urinary calcium excretion in adolescent girls. The improved bone mass accumulation found in a study of calcium-supplemented twins in Indiana, at an intake close to 47.5 mmol/day (Andon et al., 1991b), points to the same conclusion.

As already noted, the RDA for adolescents was based upon an assumption of at least 50 percent absorption efficiency. Miller et al. (1988), using stable isotopes, have shown that the value is actually closer to 35 percent, or only very slightly higher than found in adults. My own experience in nearly 100 slightly older women (19 to 25 years of age), using radioactive tracer methods, is consistent, i.e., mean absorption efficiencies ranging from 30 to 35 percent. These absorption findings, too, suggest that the requirement for adolescents and young adults may be higher than previously estimated.

In addition, the threshold may be very different for other ethnic groups. The calcium protective effect found in the Hong Kong study of Lau et al. (1988) occurred at intakes in the range of 2.5 to 10 mmol. Since full metabolic studies comparable to those performed in Caucasians (e.g., Charles, 1989; Hasling et al., 1990; Heaney et al., 1975) have not been performed in Chinese, it is not possible to say how effectively they absorb or conserve calcium. It might instead simply be that, as with many nutrients and hormones, the largest discernible response to a higher exposure is found at the lower end of the intake range. Extensive studies have not been conducted in other populations in the U.S.

**E. TIME COURSE AND DURATION OF EFFECT**

Calcium is a stable nutrient. Once deposited in bone it endures as long as the bone itself lasts. As noted elsewhere, bone serves as the calcium reservoir for the needs of all other systems. From the standpoint of the non-skeletal tissues that reservoir is effectively inexhaustible. The concern about calcium and bone health lies precisely in the fact that one and the same tissue (bone) has both this primitive reservoir function and an evolutionarily late, mechanical/structural function as well. The latter is routinely sacrificed to the former when dietary sources of calcium are inadequate to offset daily excretory losses. For no other nutrient has the reservoir acquired this kind of function. In that sense, therefore, the daily need for calcium is absolute. Any depletion of the reservoir weakens the skeleton.
F. POPULATIONS TO WHICH SCIENTIFIC EVIDENCE CAN BE GENERALIZED

One metabolic study included Caucasian male children (Andon et al., 1991b) and several epidemiological studies included adult Caucasian males (e.g., Cooper et al., 1988; Holbrook et al., 1988; Kelly et al., 1990; Wickham et al., 1989). Additionally, subjects in one study were Chinese living in Hong Kong (Lau et al., 1988) and in another were Japanese women (Lacey et al., 1991). But except for these few, the majority of the studies, whether metabolic, observational, or experimental, have focused on Caucasian females. The Hong Kong study, as already noted, found the same fracture protection benefit for higher calcium intakes as in most of the Caucasian studies, but the effect was found at a much lower intake than observed in Caucasians.

Hence, it must be stressed that the data concerning level of intake required for bone health can be safely generalized only to Caucasian females. This is not simply because that is the group from which most of the data were derived, but also because, as noted elsewhere in this report, both Orientals and American blacks give evidence either that the benefit operates at different intake levels or that their calcium economies respond differently to variations in intake.

G. DEPENDENCE OF BENEFICIAL EFFECTS ON OTHER CHARACTERISTICS OF THE DIET AND INFLUENCE OF OTHER DIETARY OR NUTRITIONAL FACTORS

1. Overview

Bone consists mainly of extracellular material, with an average life for any given unit volume in mature or older adults of 8 to 12 years. Previously formed, mature bone is almost totally insulated from the chemical, hormonal, or nutritional influences that affect soft tissues more directly. It can be resorbed to offset current excretory losses of calcium and probably also to buffer excess acid loads. (See, for example, Adams et al., 1979.) If not resorbed, previously formed bone is very little affected by factors that would profoundly interfere with other tissue functions. Thus, bone tends to average out non-calcium nutritional problems, particularly in the adult, when fractional remodeling is relatively small. As with growth rings in trees, there can be bad seasons, but they affect only current cell work, not structures previously formed under better conditions. Furthermore, defects in bone deposited today, if they express themselves at all, may do so only years later. These characteristics make non-calcium nutritional effects on bone hard to see, at least in the adult, and very difficult to study, at least insofar as other nutrients may be necessary to produce the benefit of an adequate calcium intake. Even when interactions are found, it generally remains uncertain whether they have any clinical significance.

Nevertheless, since bone formation involves cellular synthesis of protein, it follows that bone metabolism and skeletal integrity are dependent on good general nutrition just as are all cellular activities. In this sense it is important to recall that calcium is not an isolated nutrient; it occurs in many foods, always in association with other nutrients. A diet low in calcium is commonly low in other nutrients as well (e.g., Holbrook and Barrett-Connor, 1991), either because total food intake is low or because foods with high energy content such as fats or sweets have been substituted for more nutrient-dense foods. Barger-Lux et al. (1991) found that diets low only in calcium were a rarity. In a group of 89 perimenopausal females with calcium intakes below two-thirds of the RDA, roughly 90 percent were also low on one or more other nutrients -- often several.
2. **Vitamin D**

It has long been recognized that vitamin D is important for absorption of calcium from the diet. Its role lies in facilitating active transport by inducing the formation of calcium-binding protein in intestinal mucosal cells. This function is particularly important for adaptation to low intakes. However, passive transport occurs by other means, not as well elucidated, and is not dependent upon vitamin D. The proportion of absorption by the two mechanisms varies with intake and is not well characterized; at high calcium intakes it is likely that active transport contributes relatively little to the total absorbed load. Nevertheless, it is generally recognized that vitamin D status can influence absorptive performance and hence effective calcium requirement.

The principal storage form of the vitamin is 25-hydroxy vitamin D [25(OH)D], and its plasma level is the best clinical indicator of an individual's vitamin D status. Although orders of magnitude less potent than calcitriol in promoting active transport, there is evidence that it may possess physiological functions in its own right (Bell et al., 1988). Vitamin D status commonly deteriorates in the elderly, whose plasma 25(OH)D levels are generally lower than in young adults (Francis et al., 1983; McKenna et al., 1985). These elderly persons, without histological or biochemical evidence of osteomalacia, nevertheless exhibit falls in PTH levels and improvement in absorptive performance when they are given physiological amounts of supplemental vitamin D (Heaney, 1986; Krall et al., 1989). Low 25(OH)D levels in the elderly are partly due to decreased solar exposure and partly to decreased efficiency of skin vitamin D synthesis. Moreover, the elderly exhibit other abnormalities of the vitamin D endocrine system which may further impair their ability to adapt to reduced calcium intake. These include decreased responsiveness of the renal 1α-hydroxylase to parathyroid hormone (Slovik et al., 1981) and decreased mucosal responsiveness to calcitriol (Francis et al., 1984). For all these reasons there is a growing body of opinion that the requirement for vitamin D rises with age (e.g., Heaney, 1986; Parfitt et al., 1982; Suter and Russell, 1987).

3. **Fiber**

The term fiber refers to a varied group of plant polymers which are not hydrolyzed by human digestive enzymes and which therefore pass intact through the principal absorptive region of the intestine. These polymers frequently contain multiple, negatively charged groups which are capable of binding cations. In theory, therefore, they might interfere with the availability of co-ingested calcium, at least until the intestinal contents reach the colon where bacterial hydrolysis of the polymer chains may free bound cations. Contemporary diets typically contain from 5 to 15 g fiber. Current recommendations are for intakes in the range of 15 to 20 g/day. This increase, if realized, might be expected to interfere with calcium absorption. While such interference can be demonstrated in various animal models, it has been harder to show in humans. When reviewing various aspects of calcium nutrition in the elderly, a Panel on calcium nutrition and bone health in the elderly concluded that only large increases in fiber intake were likely to produce much effect (Heaney et al., 1982) and an LSRO Expert Panel, in reviewing the topic more recently (Pilch, 1987), came to much the same conclusion.

Many of the studies reviewed by these two panels were derived from measurements of calcium balance or fecal calcium, and hence were subject to the poor precision of fecal calcium measurement. More recently, isotopic tracer methods, with much greater measurement sensitivity, have allowed better quantification of the effect. Barger–Lux et al. (1989), in examining the time course of absorption from tracer data, noted that 95 percent of the calcium which will be absorbed from a mixed–food meal is absorbed by 4 to 5 hours after ingestion, and that the remaining 5 percent is slowly absorbed over the next 20 hours. This performance is consistent with the notion of release of bound calcium after entry
into the colon. At the same time it also indicates that not much calcium is made available that way in the typical adult human.

Knox et al. (1991) found that increasing the fiber content of a test meal from 0.5 to 10.5 grams (using raw wheat bran as the fiber source) resulted in a decrease in apparent calcium absorption (measured by whole-body tracer retention) from about 25 to 26 percent for the low fiber meal to about 19 to 20 percent for the high fiber meal. Weaver et al. (1991) found that 40 grams of wheat bran cereal (containing 12 grams of bran) reduced calcium absorption from co-ingested milk by about one-third (from a value of 37.5 percent to 25.8 percent). On the other hand, in the same paper it was reported higher absorption for the calcium contained in whole wheat bread than for milk ingested at a comparable calcium load. The same authors (Heaney et al., 1991; Heaney and Weaver, 1990) also report good absorbability for calcium from kale and from low phytate soybeans, both of which contain significant amounts of fiber. Consistent with this finding are the data of Wisser et al. (1991) who found no interference by a large addition (15 g/d) of a low phytate barley fiber concentrate on either calcium absorption or calcium balance in normal adults. Apparently, the various forms of fiber contained in different food sources do not interfere with calcium absorption to an equivalent extent.

It may be concluded that at least certain fiber sources, such as wheat bran, do interfere with absorption of co-ingested calcium, though the effect over an intake range typically encountered in adult diets is likely to be relatively small. The experiments of Knox et al. (1991) and of Weaver et al. (1991) are concordant and can be summarized to predict a decrease in absorbability of about 20 to 30 percent in going from a 0 to 1 gram bran fiber intake per day to roughly 30 grams per day. An adult with a basal intake of 10 grams per day, who chooses to double that intake, might therefore expect a 6 to 10 percent decrease in food calcium availability. This is not negligible, particularly if calcium intake is already low. Still, it could be easily compensated for by relatively small increases in dietary calcium intake. Finally, it must be stressed that these findings apply only to wheat bran fiber. As described above, at least some other plant fibers do not interfere at all.

4. Vitamin K

Vitamin K is known to be necessary for synthesis of osteocalcin, the major non-collagenous protein of bone. In situations of vitamin K deficiency (e.g., anticoagulant therapy), osteocalcin is under-carboxylated, and binds less well to bone mineral crystals than does normal osteocalcin. The osteocalcin found in the circulating blood of the elderly commonly exhibits under-carboxylation, and this abnormality responds to supplements of vitamin K, even when blood levels of the vitamin are themselves normal (Plantalech et al., 1990). Finally, circulating levels of both vitamin K and the menaquinones have been reported to be low in hip fracture patients, although the connection between the vitamin and bone strength, if any, remains unknown.

5. Trace minerals

Several trace minerals, notably zinc, manganese, and copper, are essential metallic co-factors for enzymes involved in synthesis of various bone matrix constituents. In growing animals, diets deficient in these elements produce definite skeletal abnormalities. Additionally, zinc deficiency is well known to produce growth retardation and other abnormalities in humans. But it is not known with certainty whether significant deficiencies of these elements occur in previously healthy adults, or at least, if they do, whether such deficiencies contribute to the osteoporosis problem. However, one very recent randomized, controlled trial involving both calcium and trace element supplementation found some additional benefit from a regimen containing both calcium and the trace metals, when compared to either calcium or trace metals alone (Smith et al., 1991).
6. **Protein and sodium**

On the negative side, the effects of excess dietary protein and sodium have already been mentioned. Both increase urinary calcium loss and hence interfere with calcium conservation in response to a restricted calcium intake. As noted earlier in Chapter III, A., protein is a powerful determinant of urine calcium, partly, at least, because of the associated increase in acid load (see, for example, Lemann et al. 1986). At least three different groups of investigators have found that a doubling of protein intake results in roughly a 50 percent increase in urine calcium loss (see Heaney and Recker, 1982).

Urine calcium rises by 1 to 2 mmol for every 100 mmol increment of ingested sodium (Nordin et al., 1991). The sodium effect is most marked at low calcium intakes and is less evident at intakes above 25 mmol/day. It is as if a large renal sodium load interferes with ability to resorb calcium from the tubular lumen under conditions when calcium is being conserved, but has less effect when excess calcium is being excreted.

7. **Phosphorus**

Phosphorus is as important for bone health as is calcium. As phosphate, it makes up roughly half the weight of bone mineral and hence must be present in adequate quantities in the diet both to mineralize and to maintain the skeleton. Phosphorus is generally present in relatively adequate quantities in the U.S. diet. For example, the 50th percentile phosphorus intake of women 20 to 29 years of age participating in CSFII 1985–86 was about 940 mg/day and phosphorus intakes of about 25 percent of women in this age group were greater than 1250 mg/day (Life Sciences Research Office, 1989). In recent years, concern of the nutrition community has centered on whether presence of excessive phosphorus in the diet might have adverse consequences (Chinn, 1981; Life Sciences Research Office, 1989).

In 1981, the FDA asked LSRO to evaluate the role of dietary phosphorus in bone homeostasis and skeletal integrity. Metabolic studies considered by an Expert Panel and summarized in the report of Chinn (1981) did not show a deleterious effect of large variations in phosphorus intake on calcium balance, irrespective of level of calcium intake. The Expert Panel concluded that although the importance of the calcium:phosphorus ratio in man was debatable and that bone loss in man from high phosphorus diets had not been demonstrated, long-term effects of high intakes were uncertain and required further study. In general, the calcium:phosphorus ratio was viewed as secondary in importance to the adequacy of calcium intake (Chinn, 1981). In 1989, another LSRO Expert Panel reached a similar conclusion, i.e., that the calcium:phosphorus ratio in humans is less important for calcium utilization than the adequacy of calcium intake (Life Sciences Research Office, 1989).

Increased phosphorus intake transiently depresses ionized calcium and leads to increased secretion of PTH, which could clearly influence bone mass. However, the effect wanes in a few days (Silverberg et al., 1986) unless calcium intake is also suppressed, in which case PTH levels remain high (Calvo, 1990). Under steady state conditions, an increased phosphorus intake reduces urinary calcium loss and increases digestive juice secretion of calcium (Chinn, 1981). The two effects are approximately equal in magnitude; hence total body calcium balance tends not to be affected.

Elevations of circulating iPTH and urinary hydroxyproline have been found in young women given high-phosphorus, low-calcium diets for four weeks (Calvo et al., 1988, 1990). However, it is unclear whether these effects are due specifically to the high phosphorus intake or to the reduced calcium
intake. Increased phosphorus intake also greatly suppresses renal synthesis of calcitriol, which could lead to decreased calcium absorption (Portale et al., 1989). At the same time, increased phosphorus intake suppresses urinary calcium loss and is used for that purpose in patients with renal stone disease. The effect appears to be direct, as it can readily be demonstrated by adjusting phosphate loads in patients on total parenteral nutrition (Wood et al., 1988).

Use of calcium carbonate as a phosphate binder in patients with end-stage renal disease is increasing because it complexes with dietary phosphorus and reduces absorption. It would seem reasonable, therefore, to infer that excess diet phosphorus would complex with calcium and reduce its absorption as well. However, metabolic studies do not confirm this inference. The absorption fraction for calcium is not affected by quite large variations in phosphorus intake (Heaney and Recker, 1982). The probable explanation for this seeming paradox lies in the quite different fractional absorption values of the two elements, particularly at the loads involved when calcium carbonate is used in patients with end-stage renal disease. Normally, most ingested phosphorus is absorbed; most ingested calcium is not. It is the large excess of unabsorbed calcium that reduces phosphorus availability. Conversely, the quantity of unabsorbed phosphorus in the chyme is usually stoichiometrically smaller than the unabsorbed calcium already available to bind with it.

Although experimental findings provide fragmentary information about the effects of dietary phosphorus on calcium regulation over the short term, the net effect of dietary-induced changes in hormonal balance on bone status over the long term has not been measured directly. However, several studies document changes in circulating levels of calcium-regulating hormones in human subjects consuming high-phosphorus, low-calcium diets. Taken together, these observations suggest that additional research is needed to resolve questions about long-term consumption of such diets on bone status.

Although low phosphorus intake is not likely to occur in the United States (Life Sciences Research Office, 1989), low phosphorus intake may limit the body's utilization of calcium for building and remodeling bone. According to NHANES II, only about 10 to 15 percent of women aged 65 to 74 have phosphorus intakes less than two-thirds the RDA (Carroll et al., 1983). The proportion is probably higher for the older elderly, whose status was not assessed in the earlier NHANES I. Low phosphorus intakes lead to excessive urinary calcium loss and hence could aggravate the effect of low calcium intakes. Conversely, as already noted, large calcium supplements will lower absorbed phosphorus and, in individuals who already have low intakes, this effect could produce phosphate deficiency. Individually, these interactions are generally well studied, but taken together in the old elderly, who may have other problems (such as declining renal function, which will affect ECF phosphorus levels), they present complexities which have not been adequately explored.

H. SIGNIFICANT SOURCES OF CALCIUM

Calcium is widely distributed in many foods. In Western diets the most prominent sources are dairy products and green, leafy vegetables, with certain nuts and shellfish playing a smaller role. Further sources include lime-processed tortillas, calcium-set tofu, and calcium-fortified foods.

In foods, calcium is associated with a variety of oxygen-containing, negatively charged groups, principally carboxyl and phosphatic, e.g., citrate, pectins, phytate, and phosphoproteins. Absorbability from various food sources varies modestly around the mixed food performance described earlier (Chapter III. A.), with dairy sources generally in the middle of the range, high phytate vegetables slightly below the middle, and low phytate vegetable sources above (Heaney et al., 1991; Recker et al., 1988). Spinach, and possibly other high oxalate sources, exhibit very poor absorbability (Heaney et al., 1988);
but spinach is clearly the exception, with most vegetable greens exhibiting superior calcium absorbability (Heaney and Weaver, 1990).

Sources commonly under-reported are calcium-containing antacids, as well as a variety of medications and nutritional supplements that contain calcium not for its nutrient value, but as an often unlisted, "inert" excipient (Heaney et al., 1990a). Such calcium is found most often in various health store nutritional supplements, but it is also found in over-the-counter and prescription pharmaceuticals. Tablets sold for their content of selenium, zinc, folic acid, para-aminobenzoic acid, "vitamin B15", and "vitamin B50", in our experience, contain from 0.5 to 2.5 mmol of calcium per tablet; royal jelly contains nearly 3 mmol. Conjugated estrogens contain from 0.5 to 1 mmol, and various psychopharmaceutic preparations, from 0.4 to 1 mmol per tablet. These are only a few examples of the calcium content of tablets consumed by our study subjects; a systematic study of this matter has not been done. The bioavailability of these calcium sources is not known, and individually their contents may seem relatively small. However, in some of our subjects, calcium from these sources has totaled to as much as 15 to 20 mmol per day and comprises one-half to two-thirds of their total calcium intakes. As previously noted, this calcium is almost always missed when estimates of intake are derived either from diet diaries or food frequency questionnaires.

I. INFLUENCES OF OTHER PHYSIOLOGIC FACTORS ON CALCIUM UTILIZATION

Bone mass and skeletal integrity are influenced by many factors besides the availability of sufficient dietary calcium. These non-calcium factors can limit skeletal utilization of calcium. Calcium is to bone mass as iron is to hemoglobin mass. Both are necessary and can be limiting; neither is sufficient alone.

1. Genetics

Genetics is clearly a major influence (Christian et al., 1989; Kelly et al., 1991; Pocock et al., 1987). Some who have studied heritability maintain that as much as 80 percent of the variation in bone mass in a healthy adult population is genetically based, with all other factors, including exercise, nutrition, and life-style, sharing the remaining 20 percent. Whether that precise partition is even approximately correct is not important, since the non-genetic arena of variability is the space within which environmental influences operate. Even if that space is as small as 20 percent of the total adult variation, that does not mean that environmental influences are therefore unimportant. Johnston and Slemenda (1991), for example, have calculated that a 5 percent difference in peak bone mass will result in a 40 percent decrease in low-trauma fractures. In any event, genetic influences on bone are not foreseeably controllable. Hence any concern for the relationship between calcium intake and skeletal status must be confined to that component of variability in bone mass which is susceptible to environmental influence.

2. Mechanical loading

Mechanical loading of the skeleton is perhaps most important of all the adjustable factors regulating bone mass. In all mammals studied to date, and in all skeletal regions examined, bone sensitively adjusts its mass up or down so that deformation under routine loading is in the range of 1000 to 1500 microstrain (Rubin and Lanyon, 1982). When loading calls for a local increase in mass, a calcium source is required. If sufficient calcium is not made available from the diet, bone-remodeling balance is adjusted in various skeletal regions so as to shift calcium from less heavily loaded to more heavily loaded bones, just as occurs (though for a different reason) during antler formation in deer.
However, while calcium is required for an increase in mass in response to increased loading, calcium will not prevent bone loss due to disuse. Very high calcium intakes may slow the rate of development of disuse atrophy, but there is no evidence that they alter the new steady state bone mass toward which the bone is adjusting itself. On the other hand, there is evidence that calcium deficient diets can aggravate bone loss from regions subjected to reduced loading (Weinreb et al., 1991; Wical and Brussee, 1979).

The interaction of calcium and mechanical loading is thus asymmetrical; calcium surfeit will neither increase bone mass beyond levels dictated by current mechanical usage nor prevent bone loss due to disuse. Calcium deficiency can also aggravate disuse atrophy.

3. **Gonadal hormones**

The loss of gonadal hormones, as following female menopause or castration in males, results in a substantial downward adjustment in bone mass amounting, in individuals of normal weight, to about 15 percent of the bone mass present at the time of hormone loss. This topic was reviewed by Heaney (1990). There is abundant evidence that high calcium intakes have little or no effect on this loss, whether given as supplements at menopause or as a part of a life-long high intake (e.g., Dawson–Hughes et al., 1990; Ettinger et al., 1987; Hansen et al., 1991; Riis et al., 1987b). Some scientists have suggested that this menopausal loss is an analog of disuse atrophy. In any event, during both processes the downward revision in bone mass releases sufficient calcium to meet most physiological needs. Thus, until the new equilibrium mass suited to the hormone-deprived state is approached (a period of about five years), there effectively may be no external calcium requirement. During that time high calcium intakes will exert no detectable effect. This is precisely what most of the studies that have looked at this question have found (e.g., Dawson–Hughes et al., 1990; Ettinger et al., 1987; Riis et al., 1987b). That this unresponsiveness to calcium is confined to this readjustment period is shown both by the positive effect of calcium found in older women (see Table 2) and most pointedly within the study of Dawson–Hughes et al. (1990). In that study women more than five years postmenopausal exhibited a positive effect of increased calcium intake whereas the same calcium supplement produced no effect at all in women from zero to five years postmenopause.

4. **Thyroid hormone**

Thyroid hormone, if present in excess, also exerts potent and potentially troublesome effects on the skeleton. In addition to increasing skeletal turnover, thyroid hormones decrease calcium absorption efficiency, increase excretory loss through the kidney and digestive secretions (Mosekilde et al., 1990), and lead to bone loss. It is not clear whether the bone loss is caused by the external negative balance or vice versa. Nevertheless, the effect on bone status seems clear. Several recent reports have shown that patients treated for hypothyroidism have significant decreases in bone mass (Kung and Pun, 1991; Paul et al., 1988; Ross et al., 1987; Stall et al., 1990), and the same is clearly true for TSH-suppressive therapy in individuals being treated for thyroid carcinoma (Diamond et al., 1991). While hyperthyroidism, untreated for any extended period, is a relatively rare phenomenon today, hypothyroidism is a common disorder, especially in women, and has often been treated with thyroid replacement in doses that many experts now consider excessive. A history of treated hypothyroidism is a common finding among women presenting with osteoporotic fractures (Kleerekoper, M., personal communication), but its overall prevalence in the osteoporotic population is not known. The extent to which thyroid effects can be offset by increased dietary calcium intakes is also unknown. As already noted, thyroid hormone reduces calcium absorptive efficiency from the intestine and increases excretory loss, and it is possible, therefore, that some of the thyroid effect would be compensated for by increased intake, but this remains conjectural.
5. **Gastric acid**

There is a widely held view that gastric acidity plays a role -- or is at least helpful -- for calcium absorption. This is presumably an inference from the fact that many calcium salts and ligand complexes are only weakly dissociated at neutral or alkaline pH and more extensively dissociated in an acid medium. Nevertheless, solubility of a calcium salt has been shown to have very little relationship to its absorbability (Heaney et al., 1990b), and in three different study designs acid production itself has been shown to have no detectable effect on absorption of calcium from food sources (Bo-Linn et al., 1984; Knox et al., 1991; Recker, 1985). Achlorhydric individuals do not absorb poorly soluble calcium sources when taken as pure salts on an empty stomach (Heaney et al., 1989b; Recker, 1985) but absorb the same salts normally when taken mixed with food. The reasons for the difference are unknown. While this phenomenon has implications for calcium supplement availability, it probably is not relevant to absorption of calcium from food sources.

6. **Miscellaneous factors**

While exercise/loading and gonadal hormones are probably the most important factors influencing the relationship between calcium and bone health, many others are also known to exert an adverse effect on bone. These include alcohol (which is directly toxic to osteoblasts, as it is to many other cells), smoking (through uncertain mechanisms), and a variety of drugs and co-morbid conditions, ranging from corticosteroids to diabetes mellitus. There is a tendency among both health professionals and interested consumers to view all of these (and other) agencies as somehow exerting their effect by interfering with calcium metabolism. Some do, but that is not their only or even their main effect on bone. Corticosteroids interfere with calcium absorption, and estrogen improves both calcium absorption efficiency and renal calcium conservation. But the effects on bone of most of these factors persist even after adjusting for their effects on calcium input and output. One cannot prevent alcohol damage by a high calcium intake anymore than one can prevent disuse atrophy by the same means. It seems necessary to stress the seemingly obvious, namely, that many of these agencies act independently of one another, and to a substantial extent, independently of calcium nutrition as well.

J. **SAFETY CONCERNS ABOUT REASONABLE OR HIGH CALCIUM INTAKES BY THE GENERAL POPULATION OR BY SPECIAL TARGET GROUPS**

There have been no new data published since the benchmark documents, pointing to any special risk associated with calcium intakes up to 62.5 mmol/day (e.g., RDA). In 1979, the Food and Drug Administration specified that this level of intake was safe for over-the-counter preparations (Food and Drug Administration, 1979). While calcium intakes as high as 62.5 mmol/day, taken as a nutrient, are not recommended, it should be noted that spontaneous intakes above that level are common among males 18 to 34 years of age in the U.S. (Carroll et al., 1983). Other populations, such as the Masai in East Africa, are known to consume regularly in excess of 150 mmol/day. No safety concerns about these levels of intake have arisen in either group. The principal concerns usually cited relate to two conditions: nephrolithiasis and some variant of the milk alkali syndrome.

1. **Nephrolithiasis**

It is generally accepted that any increase in calcium saturation of the urine in calcium stone formers will increase the likelihood of development of further stones, and hence any increase in calcium intake in such individuals may carry some increase in risk. It is in part for this preeminently plausible
reason that the typical medical regimen for stone formers involves a calcium-restricted diet. However, it needs to be recalled that calcium in the urine is generally not the cause of the stone, and hence one should not expect a high calcium intake per se to increase the risk of stone formation in individuals who are not predisposed thereto. A large body of metabolic evidence makes clear that, in the general population, urine calcium rises at the rate of about 1.5 mmol for a 25 mmol increment in dietary intake. Most or all multivariate models (e.g., Robertson, 1984) show that dietary calcium intake is a very weak risk factor for stones, and in some models, is of only marginal significance. This is probably mainly due to the fact that calcium at high intakes complexes food oxalate in the gut, reduces its absorption, and hence reduces the urinary oxalate load, as well. Thus, while urinary calcium rises slightly as intake goes up, urinary oxalate tends to fall. The net effect is often a fall in urinary calcium oxalate supersaturation. Nevertheless, high calcium intakes should not be recommended for individuals with a history of calcium stone formation until their calcium metabolism has been explored and the underlying mechanism for their stone disorder elucidated.

But neither is it prudent to advise global calcium restriction for all stone formers, both for the reasons just cited and, as Fuss et al. (1990b) have shown, because there is some risk that restricting calcium intake in such individuals will reduce their bone mass substantially. High fluid volume intakes, maintenance of an acid pH, control of infection, and possibly thiazide diuretics (e.g., Pak et al., 1987), constitute the preferred mode of management of recurrent stone formation. Dietary calcium restriction should probably be confined to individuals whose hypercalciuria is due to demonstrable hyperabsorption.

2. Hypercalcemia and the milk-alkali syndrome

The problem of the milk-alkali syndrome in association with calcium intake was reviewed in 1982 by a panel of experts assembled by the National Institute of Aging (Heaney et al., 1982). The conclusion then, still valid today, is that the problem is not likely to develop in the absence of systemic alkalosis, and even then, it is extremely unlikely at intakes up to 62.5 mmol/day. Kapsner et al. (1986) described a modern equivalent of the milk-alkali syndrome in heart-lung transplant patients treated with calcium in doses ranging from 100 to 250 mmol/day. Twenty-two percent of 297 transplant patients developed some degree of hypercalcemia, usually associated with systemic alkalosis. The multiple therapies involved in this context, and the likelihood that bone homeostatic function may be partially disabled in such patients, make these observations of questionable relevance to calcium intakes from natural or fortified foods ingested by healthy individuals. And, in any case, the calcium loads involved were substantially above intakes likely from natural or fortified food sources.

Most of the calcium sources available on the market today have not been extensively tested for their bioavailability. Poorly absorbed products would not create a problem of toxicity, but hyperabsorbed products might. It has been customary to assume that most calcium sources are equivalent in this regard. That may not be a safe assumption. Recker (1985) showed hyperabsorption of calcium from the citrate in achlorhydric women but not in women with normal gastric acid production. Calcium carbonate, by contrast, was hypoabsorbed in these same individuals, but absorbed equivalently to the citrate in individuals with normal acid production. The reasons for this difference between persons with and without stomach acid are unknown. However, since reduced acid production is relatively more common among the elderly, these observations emphasize the importance of measuring absorbability of calcium sources, whether used as supplements or as food fortifiers, in persons typical of the population likely to ingest the product concerned.
K. DIFFERENCES IN EFFICACY OF FOOD SOURCES OR BETWEEN FOOD AND SUPPLEMENT SOURCES

As already discussed (Chapter III. I.), most food sources exhibit comparable bioavailability, with some interference to be expected from high phytate food sources and high oxalate vegetables. Even so, a three-fold range of phytate content in tracer-labeled soybeans resulted in a range of absorbability extending only from 31 to 41 percent (straddling milk calcium absorbability of 38 percent, ingested at the same intake load) (Heaney et al., 1991). Hence, it can be said that, while there are differences among foods, most that contain useful quantities of calcium can be considered good sources of the mineral.

On the other hand, absorptive conditions do have an impact on absorbability. For example, all sources tested to date exhibit better absorbability when ingested with a meal rather than alone on an empty stomach (Heaney et al., 1989b). Less soluble preparations, such as the carbonate and phosphate salts will, in some individuals, be very poorly absorbed on an empty stomach (Heaney et al., 1989b), even though those individuals have the capacity for normal gastric acid production. This effect may be the explanation, for example, of the finding by Dawson-Hughes et al. (1990) that calcium carbonate was less effective than calciumcitrate-malate in slowing bone loss in postmenopausal women. In their study, both types of supplements were given in just a single daily dose, at bedtime.

A more important question relates to the comparison of food and supplement calcium sources. Here the chemical form or solubility of the supplement makes little difference (Heaney et al., 1990b). The physical form of the salt and the formulation of the tablet, however, are critical. Different calcium carbonate crystal preparations have exhibited mean absorbabilities ranging from 25 to 41 percent. Pharmaceutical formulation is yet another issue. One of the benchmark documents (Food and Drug Administration, 1989) specifically dealt with the problem of poor pharmaceutical formulation. Tablets so poorly formulated that they fail to disintegrate under simulated gastric conditions appear to be widely distributed in the U.S. market.

L. CRITICAL GAPS IN KNOWLEDGE

While much remains to be learned about bone biology, many of these basic science issues are not directly relevant to the nutritional relationship between calcium and osteoporosis. Perhaps the most important issues yet to be solved in regard to calcium nutriture can be listed as follows:

- Precisely what is the intake level at each age that is required to ensure that homeostatically mediated bone breakdown is neither limiting accumulation of genetically programmed bone mass (in the young) nor contributing to age-related loss (in the mature)?

- How long is the window of opportunity open for the repair of skeletal deficits caused by inadequate intake during childhood and adolescence?

- How can we recognize, by reasonably available testing procedures, the presence of calcium deficiency?

- How important is the reduction of bone mass that is produced by intermittent periods of reduced skeletal loading? To what extent is such bone loss reparable on resumption of normal physical activity? What is the calcium intake requirement to support such repair?
Two additional gaps, relating not so much to basic knowledge as to practical human engineering, can be cited:

- What strategies may be employed to increase the calcium nutrient density of foods in the U.S. diet to compensate both for the decline in total nutrient intake and for the qualitative shift in types of foods that has occurred in our population over the past 40+ years?

- How can we make available to practitioners and nutritional scientists a practical test of calcium absorptive performance? The technology is available and the methods tested. However, at present the technology is not used by clinical chemistry laboratories.
IV. CONCLUSIONS ON WEIGHT OF EVIDENCE

The weight of the evidence supports the hypothesized relationship between calcium intake and bone health, as expressed both in increased bone mass and in reduced fracture risk. This statement would be true even without reference to the special problems alluded to in Chapter III.C. Those problems, to the extent operative, degrade the evidence that can feasibly be produced in observational studies. The fact that the evidence seems clear even in the face of those problems thus makes the conclusion more likely.

At the same time, it is important to stress both that osteoporosis is a multifactorial disorder and that inadequate calcium intake is only one of several interacting factors that determine whether low-trauma fractures will occur. All that an adequate calcium intake can insure is that inadequate calcium status will neither be causing skeletal weakness in its own right nor aggravating the weakness produced by other causal factors. Furthermore, an adequate calcium intake cannot be expected to prevent or reverse the bone loss and fragility due to other factors. Calcium is a nutrient and the only disorder it can be expected to alleviate is calcium deficiency. The evidence indicates impaired calcium status, if not calcium deficiency, per se, is prevalent in the adult North American population and that it contributes to the nation's osteoporotic fracture burden.
V. BIBLIOGRAPHY*


* This bibliography contains all reference citations that are either in the text or the tables or both.


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APPENDIX

CRITERIA FOR INCLUSION OF ARTICLES IN APPENDIX TABLE

Articles in peer-reviewed journals related to the topic of this review were selected primarily on the basis of date and content. In general, papers appearing in 1987 or thereafter were included, provided that they presented original data from studies in humans. Certain items tabulated for the sake of completeness may not have been cited in the body of the text if their weight or relevance did not add significantly to development of the author's argument. Reviews have not been listed except as they included new data or useful meta-analyses.
### Appendix Table: Studies Addressing the Relationship Between Bone Status and Calcium Intake, Absorption, or Excretion

<table>
<thead>
<tr>
<th>Reference (author, date)</th>
<th>Study Design</th>
<th>Number and Description of Subjects</th>
<th>Duration of study</th>
<th>Source and Identity of Test Material</th>
<th>Dosage of Test Material Used</th>
<th>Base Diet</th>
<th>Additional Treatments</th>
<th>Other Factors Affecting Interpretation of Data</th>
<th>Results</th>
<th>Assessment of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham &amp; Grewal, 1990</td>
<td>Intervention, prospective trial</td>
<td>26 ¥ (19 supplement, 7 “controls”)</td>
<td>6–12 mo</td>
<td>Multivitamin, multimineral supplement</td>
<td>Ca 500 mg Mg 600 mg</td>
<td>Ca-restricted</td>
<td>Estrogen (ERT) or estrogen plus a progestogen (HRT)</td>
<td>Not randomized, compliance not assessed</td>
<td>Not blinded</td>
<td>Supplemented individuals gained bone at calcaneus</td>
</tr>
<tr>
<td>Andon et al., 1991a</td>
<td>Observational, cross-sectional</td>
<td>131 postmeno-pausal ¥ split into 2 groups at mean Ca intake. Time postmeno-pausal 18 yr</td>
<td>N/A</td>
<td>Self-selected diet, assessed by food frequency questionnaire</td>
<td>N/A</td>
<td>N/A</td>
<td>ERT in some</td>
<td>Convenience sample (not population based)</td>
<td>Vertebral bone mineral density (BMD) (L2–4) significantly lower in ¥ with Ca intakes below mean</td>
<td>Current intake is a weak surrogate for lifelong intake</td>
</tr>
<tr>
<td>Andon et al., 1991b</td>
<td>Intervention, randomized, controlled trial (RCT) double-blind</td>
<td>45 identical twin pairs, age 8.8 yr at entry</td>
<td>3 yr</td>
<td>Calcium-citrate-malate (supplement in form of tablets)</td>
<td>1000 mg</td>
<td>904 mg ± 206</td>
<td>None</td>
<td>Varying rates of growth, some became pubertal during study</td>
<td>Significantly greater increase in radial BMD in supplemented twin relative to control</td>
<td>Design did not address the question of whether benefit was merely an acceleration</td>
</tr>
<tr>
<td>Angus et al., 1988</td>
<td>Observational, cross-sectional</td>
<td>169 white ¥, aged 23–75 yr 89 premeno-pausal 71 postmeno-pausal Split into 3 Ca intake groups</td>
<td>N/A</td>
<td>Self-selected diet</td>
<td>mean c. 740 mg/d</td>
<td>None</td>
<td>Some on ERT?</td>
<td>No differences in mean BMD at spine (L2–4), hip, or forearm, among any of the intake groups, either pre- or postmenopausal</td>
<td>Current intake may be a weak surrogate for lifelong intake. Current intake assessed by 4-d weighed intake</td>
<td></td>
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<tr>
<td>Bachrach et al., 1990</td>
<td>Observational, case-control</td>
<td>18 ¥ with anorexia 25 controls</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>590 mg in anorectic patients, 1000 in controls</td>
<td>N/A</td>
<td>Multiple nutritional and endocrine deficiencies in anorexia nervosa</td>
<td>Bone mineral content (BMC) at spine and total body reduced in anorexia nervosa (c. 20–25%)</td>
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<tr>
<td>Reference (author, date)</td>
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<td>Number and Description of Subjects</td>
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<td>Base Dose</td>
<td>Additional Assessment of Study</td>
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<tr>
<td>Baron et al., 1989</td>
<td>Intervention, RCT (not blinded)</td>
<td>65 premenopausal 2, 30-42yr</td>
<td>Dairy sources</td>
<td>3 yr</td>
<td>500-600 mg Ca 890 mg</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>No decrease in forearm BMD in 18 mo.</td>
<td>Increased bone mass only at 18 mo.</td>
</tr>
<tr>
<td>Byrne et al., 1987</td>
<td>Observational, prospective</td>
<td>8 lactating 8 with dietarily mean Ca intake of controls 670 mg</td>
<td>Self-selected Ca 650 mg</td>
<td>6 wk</td>
<td>Ordinary foods</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>24-hr mean PTH, serum, calcium, phosphorus, higher with experimental diet</td>
<td>Bone mass not assessed. PTH change uncertain. Baseline PTH increased significantly.</td>
</tr>
<tr>
<td>Calvo et al., 1988</td>
<td>Intervention, RCT</td>
<td>8-18 yr 8</td>
<td>10 d</td>
<td>N/A</td>
<td>Control: Ca 620 mg P 930 mg</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Cannot tell whether PTH change is due to increased Ca intake</td>
<td>N/A</td>
</tr>
<tr>
<td>Calvo et al., 1990</td>
<td>Intervention, within-subject comparison</td>
<td>15 yr, 16-25 yr</td>
<td>High P, low Ca diet</td>
<td>4 wk</td>
<td>Experiment: Ca 420 mg P 1600 mg</td>
<td>Exp diet: Ca 800 mg P 900 mg</td>
<td>Control diet: Ca 620 mg P 930 mg</td>
<td>N/A</td>
<td>N/A</td>
<td>Attempted to deal with the problem of baseline Ca intake.</td>
</tr>
<tr>
<td>Calloy et al., 1988</td>
<td>Observational, cross-sectional</td>
<td>176 postmenopausal - ERT</td>
<td>N/A</td>
<td>6 mo</td>
<td>Self-selected Ca intake, assessed both for present and during treatment</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Group with high current and post menopausal BMD than all other groups.</td>
<td></td>
</tr>
<tr>
<td>Chan et al., 1987</td>
<td>Prospective controlled trial, post-partum</td>
<td>48 lactating 8 (86 infants - 22)</td>
<td>Dairy products</td>
<td>16 wk</td>
<td>900 mg control, 1800 mg exp.</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Method of assignment not specified. Ca groups unchanged.</td>
</tr>
</tbody>
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<th>Assessment of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy et al., 1987</td>
<td>Intervention</td>
<td>193 elderly French ♂ and ♀</td>
<td>6 mo</td>
<td>Calcium gluconolactate</td>
<td>1000 mg Ca/d</td>
<td>524 ± 172 mg/d</td>
<td>20 μg/d Vit D&lt;sub&gt;2&lt;/sub&gt;</td>
<td>25(OH)D and serum Ca low before treatment, iPTH and alkaline phosphatase high. All normalized on treatment. Response greater in housebound/institutionalized. D-deficiency and low Ca intakes common in elderly, leading to increased PTH-mediated bone resorption</td>
<td>Randomization not mentioned</td>
<td></td>
</tr>
<tr>
<td>Chow et al., 1987</td>
<td>RCT</td>
<td>50 ♂, 50–62 yr</td>
<td>1 yr</td>
<td>Exercise</td>
<td>500–1000 mg</td>
<td></td>
<td></td>
<td>Central bone mass increased in exercising groups</td>
<td>Did exercise cause increased food (&amp; Ca) intake? Typical N. American Ca intake sufficient to support exercise-induced bone gain</td>
<td></td>
</tr>
<tr>
<td>Clark et al., 1990</td>
<td>Observational, cross-sectional</td>
<td>76 pregnant ♀</td>
<td>20–30 wk of gestation</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected</td>
<td>N/A</td>
<td>Varying degrees of periodontal disease present in subjects. Probably mixed racial group</td>
<td>Alveolar bone loss greater with high Ca intake (NS)</td>
<td>Estimates of nutrient intake by 24-hr recall &amp; FFQ gave very different results</td>
</tr>
<tr>
<td>Coe et al., 1988</td>
<td>Intervention</td>
<td>7 pts with idiopathic hypercalciuria</td>
<td>3–6 mo</td>
<td>Thiazides</td>
<td>580–729 mg/d</td>
<td></td>
<td></td>
<td>Thiazides reduced urine Ca substantially and improved Ca balance by + 88 mg/d</td>
<td>Duration of treatment sufficient to get past most transients Consistent with data of Fuss et al. (1990a,b) Hypercalciuria can be a cause of Ca deficiency</td>
<td></td>
</tr>
<tr>
<td>Reference (author, date)</td>
<td>Study Design</td>
<td>Number and Description of Subjects</td>
<td>Duration of study</td>
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<tr>
<td>Cooper et al., 1988</td>
<td>Observational, case-control</td>
<td>300 6 &amp; 8 with hip fracture; 600 age- &amp; sex-matched controls</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>Ca intake estimated from consumption of only 6 food items</td>
<td>No relation of Ca intake to hip fracture in 8, protection in 6 at high intakes</td>
<td>Intake estimate method seriously flawed - not validated by investigators</td>
<td></td>
</tr>
<tr>
<td>Cunningham, 1990</td>
<td>Meta-analysis</td>
<td>49 studies</td>
<td>Varied</td>
<td>Varied</td>
<td>Varied</td>
<td>Ca intake had a consistent protective effect against postmenopausal bone loss, cross-sectional data show weak positive association of Ca intake and bone mass</td>
<td>Only formal meta-analysis on this topic to date</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dawson-Hughes et al., 1987</td>
<td>Observational, cohort</td>
<td>76 healthy postmenopausal 6</td>
<td>7 mo</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dawson-Hughes et al., 1990</td>
<td>Intervention, RCT double-blind</td>
<td>301 healthy postmenopausal 6</td>
<td>2 yr</td>
<td>Calcium-citrate-malate; CaCO₃</td>
<td>500 mg</td>
<td>Self-selected, all &lt;650 mg/d Ca</td>
<td>Ca supplemented given as single dose at bedtime, timing would produce less good absorption for CaCO₃ than for CCM</td>
<td>Ca-supplemented 6 lost no bone at most sites, unsupplemented 6 lost bone, within unsupplemented group, loss inversely proportional to intake, no effect of Ca supplement within first 5 years postmenopausal</td>
<td>Largest study of its sort ever published, good investigational design</td>
<td></td>
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<tr>
<td>Elders et al., 1989</td>
<td>Observational, cross-sectional</td>
<td>286 6, 46-55 yr</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected; median &gt;1000 mg/d</td>
<td>Spine BMD significantly lower in 6 with lowest tertile Ca intake; no effect in early postmenopausal 6</td>
<td>Intake estimated from FFQ, validation not given</td>
<td></td>
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<tr>
<td>Elders et al., 1991</td>
<td>Intervention, RCT</td>
<td>295 healthy peri-menopausal Dutch ♀</td>
<td>2 yr</td>
<td>CaCO₃</td>
<td>1000 and 2000 mg/d</td>
<td>1150-high by U.S. standards</td>
<td>N/A</td>
<td>Possibly reflects Kanis' (1989a) &quot;pharmacologic&quot; effects of high Ca intake. Apparent gain at 1 yr in highest intake group probably remodeling transient</td>
<td>Ca supplement decreased bone loss in step-wise fashion in all ♂; loss still present in early menopause; loss abolished in late menopause and in premenopause</td>
<td>Good subject monitoring. Not blind</td>
</tr>
<tr>
<td>Ettinger et al., 1987</td>
<td>Intervention controlled trial, not randomized</td>
<td>73 early postmenopausal ♀</td>
<td>2 yr</td>
<td>Estrogen – 2 levels, CaCO₃ &amp; no treatment</td>
<td>0.3 &amp; 0.625 mg estrogen, 1000 mg Ca</td>
<td>258–994 mg/d in untreated</td>
<td>N/A</td>
<td>Patients self-selected one of four treatment regimens, immediate postmenopausal period</td>
<td>Ca alone did not affect bone loss, 0.625 mg estrogen blocked it completely, as did 0.3 mg estrogen plus Ca</td>
<td>No 0.3 mg estrogen group alone for contrast</td>
</tr>
<tr>
<td>Eyberg et al., 1986</td>
<td>Observational, cross-sectional</td>
<td>45 growing black children</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>under 250 mg/d Ca</td>
<td>N/A</td>
<td>Ca intake from age 6 to 16 positively correlated with BMD, low intakes produced hypocalcemia, no hypocalcemia age 3 to 5</td>
<td></td>
<td>Nutritional, Ca-deficiency rickets?</td>
<td></td>
</tr>
<tr>
<td>Fujita, 1990</td>
<td>Intervention, controlled trial</td>
<td>Elderly ♀ 12 with osteoporosis, 21 controls</td>
<td>2 yr</td>
<td>CaCO₃ (oyster shell electrolyte)</td>
<td>900 mg</td>
<td>600 mg?</td>
<td>Not described</td>
<td>Radial BMD increased slightly at 12 and 24 mo in treated subjects, no change in spine</td>
<td></td>
<td>Many test sampling units, no difference between 6 and 24 mo</td>
</tr>
<tr>
<td>Fuss et al., 1990a</td>
<td>Observational, cross-sectional</td>
<td>32 ♀ stone-formers 32–70 yr, (18 with hyperparathyroidism)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Low Ca diet in 18 idiopathic stone-formers</td>
<td>Urine Ca elevated in both groups, idiopathic stone-formers may be abnormal in other ways</td>
<td>Radial BMC reduced in both groups</td>
<td></td>
<td>Low bone mass probably due to combination of increased urine calcium and decreased intake</td>
</tr>
<tr>
<td>Fuss et al., 1990b</td>
<td>Observational, cross-sectional</td>
<td>123 ♀ stone-formers</td>
<td>N/A</td>
<td>63 on free diet, 60 on low Ca diet</td>
<td></td>
<td></td>
<td></td>
<td>Low radial BMC in idiopathic stone formers, lower still in those on restricted Ca diet</td>
<td></td>
<td></td>
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<tr>
<td>Gallagher &amp; Goldgar, 1990</td>
<td>Intervention, controlled trial double-blind</td>
<td>50 postmenopausal ♀</td>
<td>2 yr</td>
<td>calcitriol</td>
<td>0.50–0.75 μg/d</td>
<td>Adjusted to c. 1000 mg/d Ca</td>
<td></td>
<td></td>
<td>BMD at spine and total body rose slightly on calcitriol, fell on placebo</td>
<td>A way to get extra Ca into body?</td>
</tr>
<tr>
<td>Gallagher &amp; Riggs, 1990</td>
<td>Intervention, 3 controlled trials, within-subject comparisons</td>
<td>74 ♀ with postmenopausal osteoporosis</td>
<td>2 &amp; 3 yr</td>
<td>calcitriol</td>
<td>c. 0.5 μg/d</td>
<td>Not high Ca</td>
<td></td>
<td></td>
<td>Ca balance and Ca absorption improved on treatment, fracture rate fell at 1 yr in treated vs controls</td>
<td>Only 1-yr controls, difference in fracture rate too early to attribute to effect of treatment on bone mass. Balance improvement under treatment suggests some degree of Ca insufficiency</td>
</tr>
<tr>
<td>Garn et al., 1990</td>
<td>Observational, cohort</td>
<td>74 ♀ and ♂, 30–49 yr at entry</td>
<td>21 yr</td>
<td>N/A</td>
<td>N/A</td>
<td>Varied</td>
<td>N/A</td>
<td># went through menopause between measurements</td>
<td>Change in bone mass at metacarpal not related to Ca intake. Most of variance at end of study explained by bone mass at entry</td>
<td>FFQ used to estimate Ca intake, validation not given. Intake not monitored continuously (2 points only)</td>
</tr>
<tr>
<td>Halinoua et al., 1989</td>
<td>Observational cross-sectional</td>
<td>181 healthy white ♀, 20–50 yr</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected</td>
<td>N/A</td>
<td>Physical activity assessed and factored into analysis</td>
<td>Forearm BMC positively correlated with lifetime Ca intake. Most of contrast found between 1st &amp; 2nd tertiles</td>
<td>Bone mass adjusted for differences in physical activity. FFQ used; validated against a 3-d diary, but correlation is very weak</td>
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Appendix Table: Studies Addressing the Relationship Between Bone Status and Calcium Intake, Absorption, or Excretion

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<tr>
<td>Hansen et al., 1991</td>
<td>Observational, cohort</td>
<td>121 healthy postmenopausal Danish ♀, 0.5 to 3.0 yr postmenopausal on entry</td>
<td>12 yr</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected</td>
<td>N/A</td>
<td>Alcohol &amp; oral contraceptive drugs (OCD) use assessed and factored into analysis</td>
<td>Significantly greater forearm BMD in ♀ with Ca intakes above 1500 mg/d. Difference between groups persisted through the 12-yr span, though both lost same amount across menopause</td>
<td>Same population used for study of Riis et al., 1987b</td>
</tr>
<tr>
<td>Hasling et al., 1990</td>
<td>Observational, metabolic</td>
<td>85 ♀ with osteoporosis</td>
<td>7-d metabolic balances</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected</td>
<td></td>
<td>Mean requirement for Ca equilibrium was c. 34–35 mM/d (1360–1400 mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holbrook et al., 1988</td>
<td>Observational, cohort</td>
<td>957 ♂♂ ♀♀, 50–70 yr at entry</td>
<td>14 yr</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected</td>
<td>Estrogen use common in ♀ at all Ca intakes</td>
<td></td>
<td>33 hip fractures total, rel. risk significantly less in both sexes at highest tertile Ca intake</td>
<td>Number hip fractures small, so power limited</td>
</tr>
<tr>
<td>Hunt et al., 1990</td>
<td>Observational, cross-sectional, multiple regression of age, estrogen use, early life Ca intake on bone mass</td>
<td>129 U.S. ♀, 16–30 yr</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Early life Ca intake possibly associated with bone mass in ♀ with ERT, no association in ♀ without ERT Bone mass measured by single photon absorptiometry (SPA)</td>
<td></td>
<td>No validation of method for early life Ca intake</td>
</tr>
<tr>
<td>Kanders et al., 1988</td>
<td>Observational, cross-sectional</td>
<td>60 normal eumenorhic, premenopausal ♀; normal weight</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected, mean 871 mg/d Ca</td>
<td>24-hr food recall with models plus 6-d diary</td>
<td>Forearm BMC and spine BMD positively correlated with Ca intake, effect may cease above 800–1000 mg/d</td>
<td>Good tool for assessment of intake</td>
<td></td>
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<tr>
<td>Kapsner et al., 1986</td>
<td>Observational, cross-sectional, case reports</td>
<td>297 heart and lung transplant patients</td>
<td>N/A</td>
<td>CaCO₃</td>
<td>4-10 g/d as Ca</td>
<td>High dose corticosteroid therapy, cyclosporine, antibiotics, etc.</td>
<td>Complicated context</td>
<td>65 patients (22%) developed hypercalcemia; 37 were alkalotic at the time</td>
<td>Relevance to ordinary nutritional context uncertain because status of bone as a homeostatic organ probably compromised in these patients</td>
<td></td>
</tr>
<tr>
<td>Kelly et al., 1990</td>
<td>Observational, cross-sectional</td>
<td>48 normal ♂, 21-70 yr</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected, mean c. 700 mg/d Ca</td>
<td></td>
<td></td>
<td>BMD at spine and hip positively correlated with Ca intake but not in forearm</td>
<td>FFQ validated against a 4-d record</td>
</tr>
<tr>
<td>Lacey et al., 1991</td>
<td>Observational, cross-sectional</td>
<td>178 Japanese ♂; 89 pre- and 89 postmenopausal</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Pre: 458 mg/d Post: 601 mg/d</td>
<td>Current Ca intake assessed by 3-d food record, past intake by FFQ. Bone mass measured at radius by SPA</td>
<td>Current milk intake positively associated with bone mass, calculated Ca intake not associated with bone mass, either current or past</td>
<td>Both early and late postmenopausal ♂ included</td>
<td></td>
</tr>
<tr>
<td>LaCroix et al., 1990</td>
<td>Observational, cohort</td>
<td>9518 ♂ &amp; ♀ &gt;65 yr, 27% used diuretics</td>
<td>4 yr</td>
<td>Thiazide diuretics</td>
<td>Varying</td>
<td>Low prevalence of estrogen use (&lt;2%)</td>
<td>Adjusted for body weight</td>
<td>242 hip fractures. Rel. risk for hip fracture was 0.63 (CI 0.46-.88) for thiazide users</td>
<td></td>
<td></td>
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<tr>
<td>Lau et al., 1988</td>
<td>Observational, cross-sectional</td>
<td>490 Hong Kong Chinese (280 ♂, 120 ♀) with hip fractures, 800 controls</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected, Ca very low by U.S. standards, 80th percentile at only 244 mg/d</td>
<td>Ca intake reduced risk of hip fracture. Exercise also protective</td>
<td>FFQ for 9 foods; effect operating at very low level of intake</td>
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## Appendix Table: Studies Addressing the Relationship Between Bone Status and Calcium Intake, Absorption, or Excretion

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<tr>
<td>Lukert et al., 1987</td>
<td>Observational, cross-sectional, prospective</td>
<td>64 elderly ♀ &amp; ♂; 50 perimenopausal ♀</td>
<td>4 yr for prospective</td>
<td>Self-selected diet plus supplement</td>
<td>N/A</td>
<td>Elderly: 1300-1400 mg/d Perimenopausal: 924 mg/d</td>
<td>Various</td>
<td>Ca intake fell substantially over the 4-yr follow-up</td>
<td>Possible association between forearm BMD and diet Ca: P in elderly, no association found for change in BMD</td>
<td>FFQ with portion models</td>
</tr>
<tr>
<td>Lutz, 1986</td>
<td>Observational, cross-sectional</td>
<td>26 mother-daughter pairs mean ages 55 &amp; 26</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td></td>
<td></td>
<td></td>
<td>Most mothers postmenopausal, time length postmenopausal not given; some mothers taking Ca supplement (avg. 815 mg); no daughters on supplements</td>
<td>Forearm BMC weakly correlated between mother and daughter, Ca intakes not correlated with BMC</td>
<td>7-d diet diaries used. Confounding factor of rapid postmenopausal loss in mothers not dealt with</td>
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<tr>
<td>Matkovic et al., 1990</td>
<td>Observational, metabolic</td>
<td>18 ß, 14 yr balance</td>
<td>2 wk</td>
<td>Food plus CaCO₃</td>
<td>Low, intermed., &amp; high intakes</td>
<td>Matched to pre-study intake</td>
<td>N/A</td>
<td>Ca balance positively correlated with intake. Urine Ca constant, did not drop on low intake</td>
<td>Used only 3-d diet diaries to estimate pre-study intake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>28 young ß, 3 groups</td>
<td>2 yr</td>
<td>Milk or CaCO₃</td>
<td>Control: 627 mg/d, Milk: 1381 mg/d, CaCO₃: 1162 mg/d</td>
<td>N/A</td>
<td>Small sample sizes (6 controls, 20 in milk and CaCO₃ groups combined)</td>
<td>Greater increase in forearm BMC in supplemented group, but difference not significant.</td>
<td>Insufficient power</td>
<td></td>
</tr>
<tr>
<td>Mazess et al., 1991</td>
<td>Observational, cohort, cross-sectional</td>
<td>300 white ß, 20–39 yr</td>
<td>2 yr</td>
<td>Self-selected diets and OCIDs</td>
<td>Self-selected diets</td>
<td>Self-selected</td>
<td>Two 1-d diet records, at beginning and end of study</td>
<td>No association of Ca intake with either BMD or change in BMD</td>
<td>Intake assessment tool inadequate</td>
<td></td>
</tr>
<tr>
<td>McCulloch et al., 1990</td>
<td>Observational, cross-sectional</td>
<td>101 healthy ß, 20–35 yr</td>
<td>N/A</td>
<td>Self-selected diets &amp; lifestyle factors</td>
<td>Self-selected diets</td>
<td>Self-selected mean c. 800 mg/d Ca</td>
<td>OCD use not described, but probable</td>
<td>No association of calcaneal bone density with Ca intake or other lifestyle factors</td>
<td>Ca intake assessed by recall of foods with &gt;75 mg Ca/serving</td>
<td></td>
</tr>
<tr>
<td>Meier et al., 1991</td>
<td>Observational, cross-sectional; metabolic</td>
<td>67 white and 70 black premenopausal ß, normal weight</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>No OCDS for 6 mo Extensive (234 item) FFQ with validation</td>
<td>Urine Ca significantly lower in blacks than whites (20% less). Bone density at forearm &amp; spine higher in blacks. Urine Ca significantly correlated with forearm BMD after adjusting for race. No correlation of BMD (either site) with Ca intake</td>
<td>Highlights black/white differences in Ca homeostatic set points</td>
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<tr>
<td>Nelson et al., 1991</td>
<td>Intervention, controlled trial Ca–beverage randomized; Exercise according to subject preference</td>
<td>36 postmeno-pausal females; mean age 60.2 yr</td>
<td>1 yr</td>
<td>High Ca milk–based drink or placebo drink</td>
<td>831 mg/d vs. 41 mg/d in addition to self-selected diets</td>
<td>Exercise</td>
<td></td>
<td>High Ca intake had positive effect on femoral neck BMD, but not at spine, radius, or total body</td>
<td>Small sample size; limited power – only nine subjects per subgroup</td>
<td></td>
</tr>
<tr>
<td>Nordin &amp; Polley, 1987</td>
<td>Observational, cross-sectional; metabolic</td>
<td>557 postmeno-pausal females</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected</td>
<td></td>
<td>Forearm BMD positively correlated with Ca intake; negatively with urine Ca; urine hydroxyproline also negatively correlated with Ca intake</td>
<td>176 item FFQ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Observational, prospective</td>
<td>522 postmeno-pausal females</td>
<td>9 mo</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected</td>
<td></td>
<td>Role of bone loss inversely associated with Ca intake and positively associated with urine hydroxyproline and urine Ca</td>
<td>176 item FFQ</td>
<td></td>
</tr>
<tr>
<td>Nordin &amp; Polley, 1987</td>
<td>Intervention, controlled trial</td>
<td>348 postmeno-pausal females</td>
<td>9 mo</td>
<td>Diet plus Ca supplement (Sandocal®)</td>
<td>up to 1000 mg/d</td>
<td></td>
<td>Loss of bone in higher intake group</td>
<td>Design not sufficiently detailed for adequate analysis</td>
<td></td>
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</tr>
<tr>
<td>Picard et al., 1988</td>
<td>Observational, cross-sectional</td>
<td>183 premeno-pausal females, 40–50 yr</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected, mean 576 mg</td>
<td>Various lifestyle factors also evaluated</td>
<td>BMC at both spine and forearm positively related to Ca intake</td>
<td>Questionnaire plus 3-d food diary</td>
<td></td>
</tr>
<tr>
<td>Polley et al., 1987</td>
<td>Intervention, controlled trial</td>
<td>269 postmeno-pausal females</td>
<td>18 mo (9 mo pre-study observation; 9 mo on study)</td>
<td>Self-selected diets plus Ca supplement (Sandocal® or dairy product)</td>
<td>1000 mg</td>
<td>Self-selected</td>
<td>Complicated design; subjects shifted between treatment groups; randomization altered</td>
<td>Change in Forearm BMC less negative on Ca supplement</td>
<td>Uncertain whether these data are common to those of Nordin &amp; Polley (1987)</td>
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<tr>
<td>Prince et al., 1991</td>
<td>Intervention, RCT; placebo-control</td>
<td>129 Australian $ with low bone density; mean age 56 ± 4 yr</td>
<td>2 yr</td>
<td>Ca lactate-gluconate</td>
<td>1000 mg Ca</td>
<td>760 ± 152 mg/d</td>
<td>Estrogen, progesterone, and exercise</td>
<td>Mean time after menopause 5.6 ± 2.5 yr, 14% lost sampling units, single daily dose of Ca</td>
<td>Forearm bone density loss assessed by SPA slowed by Ca plus exercise and by ERT plus exercise, not by exercise alone</td>
<td>Roughly half the subjects still in the rapid loss phase after menopause, thus Ca effect obscured in some subjects</td>
</tr>
<tr>
<td>Ray et al., 1989</td>
<td>Observational, case-control</td>
<td>127,000 elderly residents of Saskatchewan, 905 hip fractures over 1984–85, 6137 population controls</td>
<td>2 yr sample</td>
<td>Thiazide use</td>
<td>Varied</td>
<td>N/A</td>
<td>Various, including other antihypertensive agents</td>
<td></td>
<td>Risk of hip fracture decreased in dose-related fashion with duration of thiazide use. No association with other antihypertensive therapy</td>
<td></td>
</tr>
<tr>
<td>Riggs et al., 1987</td>
<td>Observational, prospective</td>
<td>106 normal $, 23–84 yr</td>
<td>2.5–6.6 yr</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected mean 922 mg/d Ca</td>
<td>No ERT</td>
<td>Postmenopausal $ included, some were in immediate postmenopausal period, where bone loss known to be unrelated to Ca intake</td>
<td>No correlation of Ca intake and rate of change in BMD at forearm and spine</td>
<td>7–d diet diary; insufficient power to find likely population-level correlation</td>
</tr>
<tr>
<td>Rius et al., 1987a</td>
<td>Intervention, RCT; double-blind</td>
<td>66 early postmenopausal $</td>
<td>2 yr</td>
<td>Ca, Sandoz</td>
<td>1000 mg &amp; 2000 mg</td>
<td>Not given; population mean c. 1000 mg Ca</td>
<td>Oral or percutaneous estrogen in all 4 groups</td>
<td>4 treatment groups with varying combinations of estrogen &amp; Ca, all subjects received ERT</td>
<td>No detected benefit of Ca when added to estrogen</td>
<td>Lost 20% of sampling units during trial. Power very limited. All subjects relatively Ca-replete</td>
</tr>
</tbody>
</table>
## Appendix Table: Studies Addressing the Relationship Between Bone Status and Calcium Intake, Absorption, or Excretion

<table>
<thead>
<tr>
<th>Reference (author, date)</th>
<th>Study Design</th>
<th>Number and Description of Subjects</th>
<th>Duration of study</th>
<th>Source and Identity of Test Material Used</th>
<th>Dosage of Test Material Used</th>
<th>Base Diet</th>
<th>Additional Treatments</th>
<th>Other Factors Affecting Interpretation of Data</th>
<th>Results</th>
<th>Assessment of Study</th>
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<tr>
<td>Riis et al., 1987b</td>
<td>Intervention, RCT, double-blind</td>
<td>43 early postmenopausal ♀</td>
<td>2 yr</td>
<td>CaCO₃</td>
<td>2000 mg</td>
<td>Not given, population mean c. 1000 mg Ca</td>
<td>Percutaneous estrogen in 1 of 3 groups</td>
<td>Ca-supplemented group had proximal forearm bone &amp; total body bone mass loss intermediate between placebo and estrogen groups, Ca supplement group not different from placebo at distal forearm &amp; spine sites</td>
<td>All early postmenopausal, all relatively Ca-replete. See also Hansen et al. (1991) for cross-sectional data on population from which these subjects selected.</td>
<td></td>
</tr>
<tr>
<td>Smith et al., 1989</td>
<td>Intervention, RCT, double-blind</td>
<td>169 healthy ♂, 35–65 yr</td>
<td>4 yr</td>
<td>CaCO₃ (OscCalc-500®)</td>
<td>1500 mg planned, 1200 mg achieved</td>
<td>666/691 mg/d</td>
<td>No ERT</td>
<td>Ca-supplement significantly reduced bone loss in humerus and radius in postmenopausal subjects. Little or no effect in premenopausal ♀</td>
<td></td>
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</tr>
<tr>
<td>Smith et al., 1991</td>
<td>Intervention, RCT, double-blind</td>
<td>137 healthy postmenopausal ♀ mean age 65 yr</td>
<td>2 yr</td>
<td>Ca-citrate-malate</td>
<td>1000 mg</td>
<td>Self-selected; mean 624 mg/d Ca</td>
<td>35% on ERT. Trial included a trace mineral supplement (Zn, Mn, Cu) 4 treatment groups</td>
<td>Ca alone protected against bone loss. Ca plus trace minerals even more positive</td>
<td></td>
<td>Analysis segregated ♀ on ERT so as not to confound interpretation</td>
</tr>
<tr>
<td>Stevenson et al., 1988</td>
<td>Observational, cross-sectional</td>
<td>59 healthy postmenopausal ♀, 4 treatment groups</td>
<td>N/A</td>
<td>N/A</td>
<td>RCT for estrogen and computed tomography. Ca not one of the treatments. Effect of Ca assessed as a co-variate</td>
<td></td>
<td></td>
<td>Cross-sectional data show no difference in bone mass for high and low Ca intakes</td>
<td>Dietary intake by questionnaire. Details not supplied nor method validated</td>
<td></td>
</tr>
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<td>Thomas et al., 1991</td>
<td>Animal intervention</td>
<td>Growing rats</td>
<td>Low Ca diet during growth, followed by adequate Ca intake in some</td>
<td>0.1 and 0.5 % Ca</td>
<td></td>
<td></td>
<td>Bone repletion occurred in low-bone, sexually mature animals when diet Ca increased</td>
<td>No control animals reared on fully normal ration</td>
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<tr>
<td>van Beresteijn et al., 1990a</td>
<td>Observational, cross-sectional</td>
<td>60 healthy ‡, 3-10 yr post-menopausal</td>
<td>N/A</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>High by U.S. standards, 2/3 of subjects had &gt;800 mg/d Ca</td>
<td></td>
<td></td>
<td>No correlation between habitual Ca intake and BMC at forearm, spine, or hip</td>
<td>No effect of varying Ca intakes on bone loss by SPA; mean loss c. 8.0% for all intake groups</td>
</tr>
<tr>
<td>van Beresteijn et al., 1990b</td>
<td>Observational, longitudinal</td>
<td>154 menopausal Dutch ‡</td>
<td>up to 8 yr</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Subjects stratified by Ca intake: &lt;200 mg/d, 800-1350 mg/d, &gt;1350 mg/d</td>
<td>Observation started at menopause in all ‡</td>
<td></td>
<td>No effect of varying Ca intakes on bone loss by SPA; mean loss c. 8.0% for all intake groups</td>
<td>Annual diet monitoring in home</td>
</tr>
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<td>Wickham et al., 1989</td>
<td>Observational, case-control</td>
<td>44 hip fracture cases in a population characterized 15 years earlier; 1-4 controls for each fracture case matched for age and sex</td>
<td>Self-selected diets</td>
<td>N/A</td>
<td>Self-selected, Mean intake in ♀ 870 mg/d, in ♂ 730 mg/d</td>
<td></td>
<td></td>
<td>No association of hip fracture and Ca intake</td>
<td>7-d diet diary on entry into study 15 yr earlier</td>
<td></td>
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