Tab E

UNITED STATES DISTRICT COURT DISTRICT OF NEW JERSEY

## FEDERAL TRADE COMMISSION, Plaintiff,

v.

LANE LABS-USA, INC., CARTILAGE CONSULTANTS, INC., corporations, and I. WILLIAM LANE and ANDREW J. LANE, individuals

Defendants.

Hon. Dennis M. Cavanaugh
00CV374 (DMC)
DECLARATION OF ROBERT P. HEANEY, M.D.

I, ROBERT P. HEANEY, M.D., DO HEREBY DECLARE PURSUANT TO 28 U.S.C. SEC. 1746, AS FOLLOWS:

## I. EDUCATION, EXPERIENCE, AND TRAINING

1. As detailed in my Curriculum Vitae, attached hereto as Exhibit 1, I am a physician, with training in Internal Medicine and Endocrinology, and have spent most of my professional life in clinical research, focused primarily around issues of calcium and bone biology, beginning with my work at the National Institutes of Health in 1955.
2. From 1957 to the present I have been employed in various capacities on the faculty of Creighton University in Omaha, Nebraska, first in the Department of

Internal Medicine, School of Medicine, then as Vice President for Health Sciences, and most recently (1984 to the present) as John A. Creighton University Professor. I am also a principal in the Osteoporosis Research Center, Creighton University.
3. As set forth in detail in Exhibit 1, I have authored or co-authored 283 peerreviewed publications in the field of clinical investigation, have written or edited four books, including one on design and analysis of clinical investigations for health professionals, have written 129 chapters in major nutrition and bone biology textbooks, and have frequently been asked to contribute editorials to the leading medical journals, including those in the bone, calcium, and vitamin D fields.
4. My research activity has focused largely on defining precisely the metabolism of calcium and the calcium intake requirement, along with developing corresponding information for other nutrients that are necessary for calcium to exert its effects, or which interact with calcium in critical ways. As an instance, my work in mid-life women was the basis for the calcium intake recommendations of the 1984 Consensus Development Conference at the National Institutes of Health on Osteoporosis.

Throughout my investigative career, beginning from my experience at the National Institutes of Health in the 1950s, I have been focused on the use of isotopic calcium tracers as tools to elucidate various aspects of the calcium economy. One application of that approach has been the measurement of calcium absorption, e.g., in
the normal diet, from natural foods, from fortified foods, and from various calcium supplements. Approximately 60 of my publications in peer-reviewed journals reflect the findings of such investigations. Additionally, I have performed dozens of other studies of the absorbability of calcium for various supplement and food manufacturers, the results of which are contained in reports submitted to the commercial entities concerned, but not published formally in the scientific literature.
5. Three examples of my work, pertinent to the present issue, are as follows:

> Heaney RP, Recker RR, Stegman MR, Moy AJ. Calcium absorption in women: relationships to calcium intake, estrogen status, and age. J Bone Miner Res 4:469-475, 1989.

Heaney RP, Weaver CM, Fitzsimmons ML. The influence of calcium load on absorption fraction. J Bone Miner Res 11(5):1135-1138, 1990.

Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of
calcium as the carbonate and citrate salts, with some observations on method. Osteoporos Int 9:19-23, 1999.

In the first of these we defined the calcium absorptive behavior of normal women at mid-life, as a function of dietary calcium intake when studied under steady
state conditions. In the second we defined the acute relationship between calcium load size and the body's ability to absorb it. One general conclusion from both investigations is that, while absorption efficiency falls as calcium load size increases, the total quantity of calcium absorbed nevertheless rises with intake. In the third paper we compared the absorption of calcium carbonate and calcium citrate and found these two principal calcium supplement sources to be absorbed identically. A feature of these (and related) papers has been the defining of these relationships quantitatively.
6. In addition to the research activity described above, and as set forth in Exhibit 1, I served as a member of the Scientific Advisory Committee of the National Osteoporosis Foundation, as a member of its Board of Directors, as the Chairperson of the Study on Osteoporosis for the Office of Technology Assessment (U.S. Congress), and as a member of the Calcium and Related Nutrients Panel of the Food and Nutrition Board of the Institute of Medicine (the body that issued the most recent nutrient intake recommendations for the bone-related nutrients).
7. Also as set forth in Exhibit 1, I have been, or am currently, a member of various professional organizations related to the field of clinical nutrition and bone biology, including the American Society for Bone and Mineral Research, the International Bone and Mineral Society, the Endocrine Society, the American Society for Clinical Nutrition, and the American College of Nutrition. I am also a
fellow of the American College of Physicians. Additionally, I have been given honorary membership in the American Dietetic Association. Some of these organizations have honored me with various awards, including Fellowship in the American Institute of Nutrition, the McCollum Award of the American Society for Clinical Nutrition, the E.V. McCollum International Lectureship for the American Society for Nutritional Sciences, and the Frederic C. Bartter Award for clinical investigation of the American Society for Bone and Mineral Research.
8. I can recall two principal legal actions, relevant to the current issue, in which I served as a testifying expert. One was an action of the FTC (1996) against a supplement manufacturer, Metagenics, Inc., on whose behalf I served as an expert witness, and the other was a trial in federal court in New York City litigating a dispute between two supplement manufacturers. Additionally, in quasi-legal actions, I have several times served as an expert witness for one or the other of contending parties in actions before the National Advertising Division of the Better Business Bureau. To the best of my recollection all of these actions involved claims related to calcium absorbability from particular supplements, and the effects of the absorbed calcium on bone.

## II. BACKGROUND CONSIDERATIONS

9. A high calcium intake reduces the risk of developing osteoporosis and is an essential component of its treatment. This conclusion has been reached by at least three NIH Consensus Development Conferences, by the FDA in its permitted health claims, by the Food and Nutrition Board of the Institute of Medicine in its Dietary Reference Intakes (1997), by the Surgeon General in his 2004 Report on Bone Health, and by the 2005 Dietary Guidelines for Americans. This much is not in contention.

Calcium, from any source, once ingested, needs to be absorbed into the blood stream. ("Absorption" here means transport from the interior of the intestine into the blood.) Absorption efficiency for calcium is low. What is not absorbed stays in the gut and is ultimately eliminated in the feces. Gross absorption for typical meal sizes and loads averages about $25-35 \%$, and net absorption is generally in the range of $10-15 \%$. (The distinction is based on the fact that, in addition to leaving the gut, calcium is also entering the gut in digestive secretions and sloughed-off mucosa.)
10. Unabsorbed calcium exhibits important functionality in its own right, but for prevention and treatment of disorders such as osteoporosis, it is the absorbed calcium that is functionally important.
11. Once absorbed, calcium loses its source identity, as the other components of the salt itself (and of its formulation as a supplement) are handled separately by the body.
12. For the same amount of calcium absorbed, all calcium salts and supplements produce approximately the same effect, i.e., they share in the generic benefit of calcium, per se (see above).
13. Different brands/formulations of the same calcium salt (same in the sense of chemical identity) commonly exhibit substantially different absorbabilities. The basis for these differences is not well characterized, but, from experience with pharmacologic agents, is probably due to effects of the so-called "inert" ingredients. I have performed research in my laboratory at Creighton establishing at least a twofold difference between the least and the best absorbed formulations of the most commonly consumed salt, calcium carbonate. However, even a less well absorbed product can confer nutritional benefit so long as some of its calcium is absorbed.
14. Absorbability (bioavailability) of calcium is measured by tracer-based methods, by pharmacokinetic methods, and by pharmacodynamic methods.

- The tracer-based are the most precise and unambiguous, but require uniform distribution of tracer in the calcium source, a feature not possible for pre-formed or commercial sources.
- The pharmacokinetic methods are the gold standard for drugs, but tend to be insensitive for substances normally present in large quantities in the body anyway (such as calcium), and they also require larger than typical dose sizes in order to ensure a measurable effect. They measure mainly the rise in serum calcium that inevitably accompanies absorption of calcium from the gut into the bloodstream.
- The pharmacodynamic methods measure 1) the rise in urine calcium or the fall in parathyroid hormone (PTH) that are the consequence of the absorptive rise in serum calcium, or 2) the change in bone mass, density, or remodeling rates produced by the absorbed calcium. The pharmacodynamic methods are the least sensitive, since what they measure is influenced by many factors in addition to absorption.

15. Absorbed calcium does not so much "go to bone" as it prevents the body from continually accessing the bony calcium reserves. Calcium is lost every day through skin, digestive secretions, and urine. The purpose of daily calcium intake is to offset these losses. If absorbed calcium is not sufficient for that purpose, the body's control systems tear down microscopic volumes of bone to scavenge their calcium. However, during growth or when patients are being treated with bonebuilding drugs such as teriparatide, the calcium of diets or supplements does "go to
bone." Nevertheless, supplement use in most contexts serves mainly to protect existing bone, not to build bone.
16. Bone is continually undergoing remodeling, a process closely analogous to the structural remodeling of buildings. First, old or damaged bone is removed ("resorption"); then new bone is laid down in its place ("formation"). At a particular site, this process takes several months in older adults. The most basic purposes of remodeling are to replace damaged bone and to reshape bone so as better to fit it to resist current load patterns. Additionally, remodeling serves to release calcium into the blood stream. For this reason, remodeling will typically be high (higher than needed for structural repair) in individuals with low calcium intakes.
17. Volumes of bone undergoing remodeling, contain little or no mineral (i.e., the calcium salt that makes bone hard), and hence this bone is not detected by the usual clinical methods (DXA) for assessing bone mass or density (BMD). If bone remodeling activity increases (for whatever reason), measurable bone mass declines, and if remodeling decreases, measurable bone mass increases. But actual bone quantity changes little if at all with such changes in remodeling activity (although the bone becomes locally more dense).
18. Because of the asynchrony of remodeling (resorption first, followed by formation later), a decrease in remodeling activity (such as might be produced by calcium, vitamin $D$, or several of the bone-active pharmacologic agents) results in an
apparent increase in bone mass. This is simply because activation of new remodeling loci is reduced, while previously activated units are coming back into service at the rate at which they were removed several weeks or months earlier. This increase continues for weeks or months (essentially for the length of the remodeling cycle), then levels off, either to the prior steady state or to a new steady state produced by the intervention. Thus these changes are referred to as "remodeling transients." They do not so much reflect gain of bone as reclaiming of what had been out of commission for remodeling. However, this is not to suggest that this change is not without benefit in many cases. If the bone removed for its calcium had been structurally sound, then removing it weakens the bone locally, and lessening of that process helps protect the skeleton.

## III. SCOPE OF WORK AND CONCLUSIONS

19. The FTC staff has asked me to read certain materials (LL650 through LL1068 (Index attached as Exhibit 2)) and evaluate, from my perspective as an expert, whether these materials substantiated certain claims, set forth below. I have read the materials provided. In broad generalities they consist of copies of full text articles published in scientific journals, copies of abstracts of articles, miscellaneous correspondence, three patents, a marketing consultant's report, and recorded interviews with Takuo Fujita, the developer of the Japanese product which is
marketed in the United States as AdvaCAL. Much of the material supplied is duplicative (some several times over). Some of it I had seen previously. ${ }^{1}$

Approximately $30-40 \%$ of the submitted evidence represents, or is based upon, articles by recognized scientists from around the world establishing the value of increasing calcium intake. In my view this evidence is not pertinent, inasmuch as it is not in dispute and, in fact, it serves as a basis for official U.S. government policy statements. That policy, stated in many formats, is that increasing calcium intake above levels prevailing in the U.S. population will confer bone benefits.

In several instances, individual reports taken from this body of generally accepted evidence are used to provide a basis for quantifying and comparing the effects of various calcium sources on bone mineral density and fracture rate, for example, as used in LL793 (Exhibit 4). In general, the results used for particular products are not representative of the totality of the evidence relating to the specific product or outcome, and in no instance were those studies performed in a way that would allow side-by-side comparison of the products concerned with respect to outcomes of interest.

An instance will serve to exemplify this problem (which occurs in this respect many times over). In LL793 (Exhibit 4), the calcium supplement, calcium-citrate-

1 In 1999 Lane Laboratories had asked me to review certain of these materials and to comment on their validity and significance. A copy of my opinion is attached as Exhibit 3.
malate (CCM), is represented as producing bone loss, whereas in the same graph, calcium carbonate and AdvaCAL are represented as producing bone gain. CCM is generally recognized to be the best absorbed calcium supplement in widespread market use, certainly at least as good as, if not better than, for example, calcium citrate or calcium carbonate. Since, as enshrined in official U.S. policy statements, the effect of calcium on bone mineral density is due entirely to the quantity absorbed, the paradoxical relationship depicted in LL793 (Exhibit 4) is not plausible. Furthermore, if one examines the paper behind the CCM figure, one notes that there was a placebo group that lost $3.5 \%$ of bone mass over two years, whereas the CCM group lost $1.25 \%$, or about only one-third as much. That represents a substantial benefit for women who would otherwise be losing a great deal more bone. By contrast, other studies of CCM in women with stable bone mass show an apparent gain in bone due to a positive bone remodeling transient (see II. Background Considerations 17-19). In brief, the results one gets from a given intervention depend heavily upon the underlying biology of the group concerned, and comparisons between products can be made only within such groups, not across groups that otherwise differ in important respects. In general, the same types of criticisms can be made about the fracture comparisons in the advertising copy in LL793 (Exhibit 4), but here there are additional problems, as well (see below).

There is a second instance, which typifies the generally poor investigational design of many of the studies involving AdvaCAL, as well as the tendency to misinterpret the results. I refer to two papers by Fujita and colleagues (LL667-671 and LL750-756). The first was published in the journal, Calcified Tissue International in 1996 (Exhibit 5) and describes results of a study that had, seemingly, been previously published in a Japanese journal (LL664-666), and had described results in individuals treated with three products, one called AAACa (presumably identical to AdvaCAL), ${ }^{2}$ calcium carbonate, and placebo, in elderly, hospitalized women with a mean age of 80 . The effects on bone mineral density of the three treatments, as set forth, for example, in Table 1A (LL668 - Exhibit 5) seemed to indicate improvement in bone mineral density in all three groups so that, by 24 months, BMD had risen by $0.049 \mathrm{~g} / \mathrm{cm}^{2}(7.8 \%)$ in the AAACa group, by 0.009 (1.5\%) in the calcium carbonate group, and by $0.010(1.6 \%)$ in the placebo group. But placebo-treated, 80 -year-old women do not gain bone over a 24 -month period, as this dataset taken at face value would suggest.

The most likely explanation for this seemingly anomalous fact is found in the numbers of patients available for measurement at each time point. The three groups, initially, contained 19, 17, and 20 individuals, respectively. By the 24-month time

2 Because formulation can have a major effect on absorbability (See II. Background Considerations 14), identity of the marketed and tested products is critically important.
point, these numbers had fallen to 5,6 , and 7 . Two points need to be made: the sickest, frailest individuals - the ones with the lowest starting BMD values - are almost certainly the ones who were lost from study; thus every time a sick individual with low BMD dropped from study, the average for the group remaining in the study rose, of mathematical necessity. Note that two-thirds to three-fourths of all the subjects entering the trial had dropped by the 30 month point. Even had that not been the case, it is not scientifically valid to compare group mean values with this type of study design. It is the within-individual change which is the appropriate variable to be evaluated, and that information is not supplied in this paper. Furthermore, even had it been supplied, the remaining sample size would have been too small to permit any kind of useful conclusion.

This same paper contains a number of internal inconsistencies, not explainable except possibly by the bias that is conferred by comparing means at different time points when the numbers of subjects in each measurement group differ (see above). Table 3A on LL669 (Exhibit 5) is a case in point. It contains values for urinary $\mathrm{Ca}: \mathrm{Cr}$ ratios in the three treatment groups. The $\mathrm{Ca}: \mathrm{Cr}$ ratio is effectively equivalent to urinary calcium excretion (with the creatinine serving to correct for incomplete collections and like errors). Urinary calcium excretion is a widely used measure to evaluate calcium absorption. It is a relatively weak and insensitive measure, and is not one that I would recommend; nevertheless, its use is based on the fact that when
one absorbs calcium, some of the absorbed calcium spills into the urine, thereby raising urine calcium. Calcium absorption is never associated with a fall in urine calcium. As Table 3A shows, however, using only the group means at the various time points, the urinary $\mathrm{Ca}: \mathrm{Cr}$ ratio falls from a pre-treatment value of 0.344 to a $30-$ month value of 0.173 in the individuals treated with AAACa. Thus the urine calcium, as reported, shows no evidence whatsoever of any calcium absorption, and without calcium absorption there cannot have been an effect on bone mineral density. But once again, the appropriate measure would have been the within-individual change, and that is not supplied by this paper. This inconsistency highlights why analysis of group means in a repeated measures design is invalid. In this case it produces blatantly implausible results. (Incidentally, all three treatment groups showed comparable "declines" in the $\mathrm{Ca}: \mathrm{Cr}$ ratio.)

No mention of fracture is made in this paper, but fractures observed in apparently the same trial are reported in LL750-756, a paper published in the Journal of Bone and Mineral Metabolism, 2004 (Exhibit 6), which is described as a "reappraisal" of the data from the study first published definitively in Calcified Tissue International (Exhibit 5). As with the earlier paper, we still have no data on within-subject changes, and the fracture figures cited are impossible to interpret since they are expressed as numbers of fractures per 1,000 subject years, without providing the number of subject years actually experienced; moreover the absolute number of
fractures is, itself, not even mentioned. Since the study duration was 2.5 years, and by the end of the study, three-fourths of the subjects had dropped out, it can be roughly estimated that there were perhaps no more than 10 actual person years of observation in each group. While the paper reports that no fractures occurred in the AAACa-treated group, a finding of zero out of 10 is actually consistent with a true fracture rate of anywhere from $0 \%$ to as high as $31 \%$. The confidence intervals for the estimated fracture rates for the three groups are not given, and should have been. In any event, Dr. Fujita himself, in his interview (LL766-773) (Exhibit 7) acknowledges that the number of subjects in this study was too small to support a claim of zero fractures.

Lane Labs also cites as support for its claims a paper published in the Journal of Bone and Mineral Metabolism in 1997 (LL672-675). There is no side-by-side comparison here with other calcium salts; hence this study cannot be used to support a claim of superiority for AAACa. This study was apparently the source of the value used in the left-hand bar graph in LL793 (Exhibit 4). In its original context, the 2.6\% improvement at 24 months is about what might be expected for any good calcium supplement. As the data in Table 2 (LL673) show, most of this change was achieved by 6 months, with very little further improvement thereafter. This is the type of behavior typically seen with the remodeling transient (see above), such as might be produced by calcium.

Finally, Lane Labs cites as support for its claims of superiority a paper published in the Journal of Bone and Mineral Metabolism in 2000 (LL676-679). This study found no significant change at the lumbar spine for any product (and no difference between products). There was a statistically significant increase in radial BMD for AAACa, but not for the other preparations, but there was no statistically significant difference between AAACa and Calcium Carbonate. Moreover, the groups were not well matched, both on age and on baseline BMD, and the sample sizes were extremely small (between 6-11 individuals per group). This study thus produced an indeterminate result. Such studies should not be done, as they are clearly underpowered, and if done, should not be published.
20. The FTC staff has asked me to evaluate the following three groups of claims:

## 21a. AdvaCAL is more absorbable than other calciums

Relatively few of the materials provided contain information with respect to relative absorbability of calcium from AdvaCAL. One such would be LL685-689, a report vaguely describing a study in parathyroidectomized rats given massive calcium loads by gastric gavage. This paper seems to be an evaluation of the value of added HAI to a product called AACa, rather than of AdvaCAL absorbability, per se. While HAI was associated with apparently higher levels of calcium absorption, there was no dose response relationship across a broad range of HAI doses ( 10,000 -fold). The
findings are thus very difficult to interpret. The same paper, by contrast, showed that in a different animal model (rats fed a low calcium diet), AACa alone was as effective as AACa plus HAI. Another paper (LL690-695) by Fukuta contains information on calcium absorbability, but the methods are not mentioned and Fig. 1 in that paper shows implausibly high elevations of serum calcium after intraintestinal injection. This portion of the Fukuta paper may have been a reference to the study cited under LL685-689, but this is not clear. There are no human studies in the body of evidence describing calcium absorbability from AdvaCAL, alone or in comparison with other calcium sources.

Nor is there evidence in the material provided me to support a claim that, in humans, AdvaCAL is 3 times more absorbable than other calciums. It is useful to bear in mind that the calcium absorption fraction for most calcium sources (including milk) at a 300 mg load is approximately 0.30 , and for a source to be 3 times as absorbable as that, the fractional absorption would have to be 0.90 (or $90 \%$ of the ingested calcium absorbed). Except in low birth weight newborns with an immature gut, no calcium absorption fractions remotely close to 0.90 have ever been reported.

I have also, independent of this action, investigated the absorbability of calcium from AdvaCAL under a contract with Lane Laboratories (Exhibit 8). This work was performed in 2000 and reported to Lane Laboratories in December of that year. Briefly, absorbability of calcium from AdvaCAL was compared to the absorbability
of calcium from Citracal ${ }^{\text {TM }}$ (Mission Pharmacal) using pharmacokinetic methods in a randomized cross-over design in 24 healthy postmenopausal women. Calcium load for the two sources was effectively identical ( $955-995 \mathrm{mg}$ ). With the pharmacokinetic methods, comparison is made between the degree of elevation of the serum calcium concentration consequent upon absorption of calcium from the gut into the blood stream. This elevation is measured as "area under the curve (AUC)". In my study, AUC for AdvaCAL was $3.148 \mathrm{mg} \cdot \mathrm{hr} / \mathrm{dL}$, and for Citracal ${ }^{\mathrm{TM}}, 4.386$ $\mathrm{mg} \cdot \mathrm{hr} / \mathrm{dL}$. (The higher value for Citracal ${ }^{\mathrm{TM}}$ indicates about $30 \%$ greater absorption of its calcium.) Converting these AUC values into absorption fractions revealed that fractional absorption for AdvaCAL was 0.218, and for Citracal, 0.284. The conclusion that can be reached from these data is that the absorption of calcium from AdvaCAL is good, but not as good as the absorption from Citracal, and certainly not superior.

21b. AdvaCAL is the only calcium product that can "build bone." AdvaCAL can increase bone mass density a specific amount. (For example, increases bone density in women by as much as 10\% a year; $13.5 \%$ increase in bone density after 24 months; $3.8 \%$ increase in bone density after 4 months; $3.2 \%$ increase in bone density for elderly women in 2 years; $2.5 \%$ increase in bone density for post-menopausal women in 2 years; those suffering from osteoporosis (ages 51-83) increased BMD by $4.5 \%$ over 3 years. AdvaCAL builds more bone than other calcium products. (For
example: Clinical studies show AdvaCAL is substantially superior to Ca Carbonate, Ca Citrate Malate and Ca Hydroxy Apatite in increasing spinal bone density in postmenopausal women and elderly women; increases bone density in post-menopausal women (approximately $2.6 \%$ over 2 years) compared with Calcium Citrate (approximately $1 \%$ over 2 years) and Calcium Citrate Malate (approximately -1.2\% over 2 years); increases bone density in elderly women (approximately $3.1 \%$ over two years) compared with Calcium Carbonate (approximately $0.8 \%$ over 2 years) and Calcium Hydroxy Apatite (approximately $1.9 \%$ over 2 years). AdvaCAL is Comparable or Superior to Rx Drugs in Building Bone.

These claims have two components: "building" bone and superiority relative to other products. No calcium source, by itself - and that includes AdvaCAL - literally builds new bone. While calcium is one of the basic components of bone, it is not a sufficient stimulus by itself to cause more bone to be formed. Individuals who are given bone active agents, particularly of the anabolic sort (e.g., Eli Lilly's Forteo ${ }^{\mathrm{TM}}$ ) do, in fact, build bone. And they need a high calcium intake in order to support that bone building. In such circumstances calcium helps build bone, but it does not do so by itself.

However, there is one sense in which the changes produced by supplemental calcium might be interpreted as building bone. Because of the reduction of remodeling which is produced by calcium supplements, there is an increase in
measurable bone mineral density, as noted above, and this could be interpreted as consistent with the concept of "building bone." But as noted in II. Background Considerations 17-19, the increase in measurable bone mineral represents bone that was actually already there, but not fully mineralized, and therefore not measurable. This is not to minimize the value of reclaiming bone that had been out of commission, for it is likely that such reclamation is in large part responsible for the reduction in fracture risk. But it is to stress the distinction between building new bone, and reclaiming bone undergoing remodeling.

With respect to the matter of superiority, there is nothing, in my judgment, in the evidence provided me, which would indicate that AdvaCAL calcium has effects that are more striking in this regard than any other calcium supplement. To the extent that one accepts the effects of calcium on "filling in the remodeling space" as being equivalent to "building" bone, then AdvaCAL shares in those effects, as do other properly formulated calcium supplement sources.

Additionally, nothing in the materials supplied me (LL650 through LL1068Exhibit 2) provides credible scientific support for the specifics of the aforementioned claims. It is possible to envision particular situations (see below) in which increases of the magnitude stated in the claims quoted above might be plausible. In general, however, they would be quite unusual.

Whether any calcium source will increase bone mass density by a specific amount depends mainly on certain features of the study participants and on study details. Also, the word "increase" needs to be more precisely defined. For example, if a group of individuals, on average, is losing bone because of inadequate calcium intake, then the use of calcium supplements will slow or stop that loss. While not technically an "increase" as would be intended in common English usage, this is nevertheless an improvement. Also, in a parallel, two-group study, the supplemented group will end up with more bone than the unsupplemented. So if the data were plotted as a bar graph, the supplemented group's BMD value would be above the unsupplemented, and might thus seem to indicate an increase. However, a higher value relative to a contrasting treatment, while useful, is not the same thing as a true "increase" from baseline.

Further, and as set forth in II. Background Considerations 17-19, calcium supplements, in common with several other bone active agents, reduce bone remodeling and produce a transient increase in measurable bone mineral. If the individuals in which a particular supplement is being tested have a high rate of remodeling, then the size of the remodeling transient will be correspondingly large, and if the basic rate of bone loss is close to zero, then this large transient will produce a measurable increase in bone mineral. This is termed "filling in the remodeling space" and does not represent so much new bone, as bringing bone that had been
under repair back into service. Nevertheless, this change is measured as an increase in bone mineral density and it is likely to result in bone strengthening.

At the same time I must also stress that, because a fraction of the AdvaCAL calcium is absorbed, it would be predicted to produce the benefits that accrue to calcium generally, and these would include the slowing or cessation of age-related bone loss, coupled with a positive bone remodeling transient.

Finally, there is no evidence in the materials supplied me to support a claim of comparability (or superiority) relative to pharmacologic agents, and I am not aware of any other evidence that would substantiate it. Most of the pharmacologic agents have been tested against a "placebo" group that actually consisted of a calcium supplement, usually in a dose on the order of $500 \mathrm{mg} / \mathrm{d}$. The reported fracture reduction values for these agents were, therefore, relative to what one would get with a modest supplemental calcium intake. In order to be approved by the FDA, they had to have exhibited statistically significantly greater effects (change in BMD and reduction in fracture) than the calcium-treated, control group. By contrast, the trials of calcium with fracture outcomes just cited used a low calcium, true placebo control. Thus the potency of calcium relative to the pharmacologic agents is unclear, as the two classes of agent have not been tested side-by-side in a properly designed trial. Nevertheless, there is a scientific consensus that calcium, while useful and necessary, is not as potent in reducing fracture risk as the bone active pharmacologic agents
taken with calcium. In my judgment, it would be potentially dangerous to tell patients at high risk for fracture that they needed only a particular supplemental form of calcium, as doing so might cause them to forego needed pharmacotherapy.

21c. AdvaCAL users have fewer fractures than users of other calcium products. AdvaCAL users can avoid fractures.(For example, $100 \%$ fracture reduction for elderly patients over 3 years; "You don't have to be in a nursing home because you broke your hip - all you have to do is take your AdvaCAL to prevent that."')

These two claims would seem to contradict one another, inasmuch as "fewer fractures" implies that AdvaCAL users would have some fractures, whereas the second claim suggests no fractures. In any event, AdvaCAL users could be expected to have fewer fractures than non-users of calcium supplements, but the evidence provided (LL650-LL1068 - Exhibit 2) does not provide evidence to substantiate a claim of superior fracture reduction. With the exception of LL667-671 (Exhibit 5), there are no randomized, side-by-side comparisons of AdvaCAL with other calcium supplements, and the evidence cited in advertisements such as LL793 (Exhibit 3) come from very different studies involving very different populations and treatment conditions. Furthermore, the figures cited for such products are not representative of the totality of the evidence with respect to the individual sources used in this comparison.

With respect to the claim of avoiding fractures, I know of no evidence, including that provided by Lane Laboratories, to substantiate a claim that patients ingesting AdvaCAL or any calcium supplement could "avoid" fractures. Indeed, as already noted, Dr. Takuo Fujita, in a recorded interview in one of the items of evidence (LL766-LL773 - Exhibit 7), himself noted, in commenting on his paper in which fractures were recorded, that the sample size was not large enough to substantiate a claim of "no fractures." I would expect that users of any absorbable calcium supplement, including AdvaCAL, will have a reduced fracture risk, but not zero. No bone active agent, nutritional or pharmaceutical, can prevent all fractures (the usual meaning of "avoid"). Adequate calcium intake, particularly when coupled with normal vitamin D status, has been reported in well-controlled studies to reduce fractures in various studies and at various skeletal sites by from 30 to $55 \%$.

Similarly, various pharmacologic agents have been shown to reduce fracture risk by roughly 40 to $70 \%$. Nothing reduces fractures by $100 \%$. Incidentally, and as noted above, it would be dangerous, in my judgment, to tell consumers at high risk for fracture that a calcium source alone provided as good fracture protection as approved pharmacologic agents.
22. Because cost is an important consideration for consumers, the FTC staff has asked me to include a paper describing a study my colleagues and I performed comparing absorbability of calcium from two marketed calcium salts, and evaluating
their relative cost-effectiveness. (Exhibit 9) In brief, calcium citrate and calcium carbonate exhibited identical absorbability, but because calcium citrate was the more expensive of the two, calcium carbonate delivered a greater amount of calcium into the body for the same dollar cost.

## IV. GENERAL REQUIREMENTS FOR RELIABLE SCIENTIFIC SUPPORT FOR DEFENDANT'S CLAIMS

23. The claim of superiority of one product relative to another requires a double-blind, randomized trial, utilizing either parallel side-by-side treatments, or a within-subject cross-over. The latter is better suited to evaluation of absorbability since it can be done in a short period of time and has lower sample size requirements, whereas the former is necessary for detection of differences in BMD or fracture rate, since these outcomes require years for their effect to become apparent. With either design, quantitative comparisons between products or treatments can be made only for products or treatments randomly allocated to participants in the same study. Moreover, when the conclusions from such a study involve changes in some measurable variable (such as fracture rate, BMD, or absorbability), it must be the changes produced under the two treatment conditions that are evaluated and tested statistically.

Having said that, there are two features of AdvaCAL which require some nuancing of the foregoing.

First, AdvaCAL is a calcium source, and, as noted in II. Background Considerations, 10-13, once calcium from a particular source is absorbed, it shares in all the benefits of calcium generally. Briefly, to claim greater bone benefits, one needs only to show greater absorbability, because, for the same ingested load, the better absorbed product delivers more calcium into the blood stream. (At the same time it is necessary to point out that virtually all calcium sources can potentially deliver the same quantity of calcium into the blood stream by the simple device of adjusting the size of the dose.)

The second issue relates to the HAI ingredient in AdvaCAL, with respect to which most of the evidence supplied me is relatively silent. If HAI were to have some bone activity in its own right, then that possibility would have to be tested in the same way that the pharmacologic agents are tested, i.e., with a large, placebocontrolled trial. On the other hand, if the activity of HAI (to the extent that such exists) is confined to promoting calcium absorption (as is implied in some of the evidence provided), then simple tests of the absorbability of AdvaCAL should suffice to evaluate such claims.

## V. CONCLUSION

24. I understand that the FTC uses a standard of "competent and reliable scientific evidence" in evaluating claims. It is my considered judgment, as an expert in this field, that no competent and reliable scientific evidence exists to support the claims cited above for Lane Laboratory's AdvaCAL. Thus, my conclusion is that the evidence provided does not satisfy the general requirements for the establishment of a claim of superiority for any product, relative to any other. While AdvaCAL can be a useful nutritional supplement, in terms of absorbability, effect on bone mineral density, and effect on fracture rate, AdvaCAL is not superior to other calcium sources.

I declare under penalty of perjury that the foregoing statement is true and correct.
Executed at Omaha, Nebraska on Qeernairy 3, 2006.


Robert P. Heaney, M.D.

## Exhibit 1

# CURRICULUM VITAE <br> ROBERT P. HEANEY, M.D. 

## Current Position:

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## Personal:

Born - November 10, 1927, Omaha, Nebraska
Religion - Roman Catholic
Marital Status - Married (Barbara Reardon Heaney, M.D.)
Children - Seven
Home Address - 5210 Burt Street, Omaha, NE 68132

## Education:

B.S., Magna cum laude (Chemistry Major), 1947

Creighton University, Omaha, Nebraska
M.D., Creighton University School of Medicine, 1951

Omaha, Nebraska
Internship - St. Louis City Hospital, 1951-1952
St. Louis, Missouri
Residency - St. Louis City Hospital
Service of St. Louis University (Internal Medicine) 1952-1953
Additional Graduate Training:
Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma American Cancer Society Clinical Fellow, 1953-1954
Public Health Service Post-Doctoral Fellowship (NCI) 1954-1955
National Institute of Arthritis \& Metabolic Diseases
Bethesda, Maryland, Clinical Associate 1955-1957

## Uniformed Service:

U.S. Public Health Service (Sr. Ass't. Surgeon) 1955-1957

## Teaching \& Administrative Appointments:

University of Oklahoma School of Medicine
Instructor, Department of Medicine, 1954
George Washington University
Clinical Instructor, Department of Medicine, 1955
Creighton University
Assistant Professor, Department of Medicine, 1957
Associate Professor of Medicine, 1960
Acting Chairman, Department of Medicine, 1960
Professor of Medicine, 1961
Chairman, Department of Medicine, 1961-1969
Head, Section of Endocrinology \& Metabolism, 1969-1971
Vice President for Health Sciences, 1971-1984
John A. Creighton University Professorship, 1984-
Creighton University
Chair, Presidential Task Force for Dominican Republic Programs, 1995-97
Chair, Presidential Task Force on Compliance Issues, 2000
Chair, Presidential Task Force on Clinical Research, 2003

## Membership in Professional Societies:

American College of Physicians (Fellow)
American Institute of Nutrition (Fellow) now American Society for Nutritional Sciences
American College of Nutrition (Fellow)
American Society for Bone and Mineral Research
American Society for Clinical Nutrition
International Conferences on Calcium Regulating Hormones, Inc.
Physicians for Social Responsibility
The Endocrine Society

## Scientific Committee Memberships \& Consultantships:

National Institute of Dental Research, Dental Training Committee, Member, 1962-1966
National Aeronautics and Space Administration, Manned Spacecraft Center, Consultant, 1964-1965
National Institutes of Health, General Medicine (B) Study Section; Member, 1966-1970; Chairman, 1970-1971
Central Society for Clinical Research, Counselor, 1966-1969
U.S. Veterans Administration, Endocrinology and Metabolism

Review Panel, Member, 1969-1972
National Academy of Sciences, National Research Council, Calcium Metabolism Review Panel, Member, 1970-1971
National Institute of Arthritis and Metabolic Diseases, Orthopaedic Training Committee, Member, 1971-1973
National Institute of Dental Research, ad hoc Committee for Review of Mineralization Research Effort, Chairman, 1973
National Aeronautics and Space Administration, American Institute of Biological

Sciences Medical Sciences Advisory Panel, Member, 1976-1980
National Institute for Arthritis Metabolic and Digestive Diseases; Arthritis, Bone and Skin Program Project Review Group; Member, 1977-1978
National Institute of Dental Research Special Grants Review Committee, Chairman, 1982-1986
The National Osteoporosis Foundation, Scientific Advisory Committee, 1986-1991; Board of Directors, 1990-2002; Emeritus Board, 2002; Co-Chair Education Committee, 2002-2005; Chair, Network Task Force, 2001-2002; Scientific Advisory Council, 2005-2008.
Nutrition Research Science Advisory Committee of the National Dairy Council, 1986-1989; Chairman, 1987-1989
Scientific Visiting Committee of USDA Human Nutrition Research Center on Aging at Tufts University, 1986-
Office of Technology Assessment, US Congress, Scientific Advisory Panel on Osteoporosis, Chairman, 1990-1994
Calcium Information Center, Scientific Advisory Board, 1991-
National Osteoporosis Data Group (NODG), 1993-
NIH. Postmenopausal Estrogen/Progestin Intervention (PEPI), Data and Safety Monitoring Board, 1991-1994
NIH, Womens' Health Initiative, Data and Safety Monitoring Board, 1993-2004
Nutrition Advisory Group/Coca-Cola Company, 1994-1995
NASA Life Sciences Advisory Sucommittee, 1994-1997
National Nutrition Advisory Council/Administration on Aging, DHHS, 1995-1997
MilkPEP Medical Advisory Board, 1994-
Panel on Calcium and Related Nutrients, Food \& Nutrition Board, NAS, 1995-1997
GlaxoSmithKline Calcium Advisory Board, 1997-2005
National Bone Health Campaign Scientific Task Force, 1999-
NAMS Consensus Opinion on the Role of Calcium in Peri- and Postmenopause, Editorial Board Chair, 2000; 2006
Duke Clinical Research Institute, Data and Safety Monitoring Board Chair, 2002-2003
Surgeon General's Report on Osteoporosis and Bone Health, Writing Committee, 2003
ConAgra Scientific Advisory Board, 2006-2008

## Educational Committee Memberships \& Consultantships:

Association for Academic Health Centers, Board of Directors, Member, 1975-1978; Program Chairman, 1977; Chairman-Elect, 1978-1979; Chairman, 1979-1980
ADA Council on Dental Education, Special Review Committee on "Dental Education in the United States 1976" Member, 1978-1979
Chairman, ad hoc Consultant Panel for Peter J. Liacouras, President, Temple University, in regard to Temple University School of Pharmacy, 1985
Pew National Dental Education Program Advisory Committee, 1984-1992
National Commission on Nursing Implementation Project, 1985-1987
Committee of Visitors, Vanderbilt University School of Nursing, 1987-

## Civic and Church Committee Memberships \& Consultantships:

Health Planning Council of the Midlands, Member, Board of Directors, 1971-1981; Member, Executive Committee, 1972-1979; Vice President, 1974-1978; Secretary, 1979
Archdiocese of Omaha: Archdiocesan Commission on Sacred Liturgy, Music, and Art; Member, 1968-1981
St. John's Parish, Omaha, Parish Council, Member 1978-1986; Chairman, 1980-1981; Member 1994-
Loyola University, Chicago, Illinois, Board of Trustees, Member, 1981-1990; Medical Center Committee 1981-1992
Omaha Safety Council, Member, Board of Directors, 1986-1989
Wellness Councils of America Medical Advisory Board, 1997-

## Editorial Boards:

Calcified Tissue (Research) International, 1966-1977, 1978-1986, 1994-1999
Journal of Clinical Endocrinology and Metabolism, 1967-1969; 2002-2006
Journal of Laboratory and Clinical Medicine, 1976-1982
BONE, (previously Metabolic Bone Disease and Related Research), 1981-1994
BONE, (merger between BONE and Bone and Mineral), 1994-
Bone and Mineral, 1985-1994
Dairy Bureau of Canada's Nutrition Quarterly, 1986-
Osteoporosis International, 1990-
European Journal of Experimental Musculoskeletal Research, 1990-
American Journal of Clinical Nutrition, 2006-2008

## Honors and Awards:

Alpha Sigma Nu
Alpha Omega Alpha
Lederle Medical Faculty Award 1960-1963
Chairman, Gordon Research Conference, (Bones and Teeth) 1966
Kappa Delta Award (American Academy of Orthopaedic Surgeons), 1970
Creighton Distinguished Faculty Award, 1974
Network for Cont. Med. Educ. Ohio State Award for the program: "Osteoporosis:
A Disorder of Bone Remodeling," 1979
Combined Health Agencies Drive of Omaha, Health Citizen of the Year Award, 1984
Creighton University, Alumni Achievement Citation, 1988
The American Dietetic Association, Honorary Membership, 1990
Third International Symposium on Osteoporosis, Copenhagen, Honorary President, 1990
Creighton University, Distinguished Research Career Award, 1991
Fellow, American Institute of Nutrition, 1993
Frederic C. Bartter Award, 1994, American Society for Bone \& Mineral Research
2000-2001 Best Scientific Paper Award, American College of Nutrition
State of Nebraska, Admiral in the Great Navy of the State of Nebraska, 2003
Institut-Candia Scientific Prize for 2003
E.V. McCollum Award, 2003, American Society for Clinical Nutrition

Laureate Award, 2003, Nebraska Chapter of the American College of Physicians

2004 North American Menopause Society Innovations in Osteoporosis Award

## Named Lectureships:

The Second Annual Drummond Lecture in Medical Ethics, St. Louis University Medical Center, 1987
The Seventh Annual Dorothy E. Vossen Lecture Series in Nursing, Creighton University, 1987
The Dean's Distinguished Lecture Series, School of Nursing, University of Pennsylvania, 1987
James F. Sullivan Lectureship, Department of Internal Medicine, Creighton University, 1992
American Dairy Science Association, First ADSA Foundation Lecture, 1993
Boyd O'Dell Lectureship, University of Missouri - Columbia, 1995
Ethel Austin Martin Distinguished Lectureship, SD State University, Brookings, 2000
Lila Wallis Distinguished Visiting Professor on Women's Health, Cornell University Medical Center, New York, 2003
$19^{\text {th }}$ Annual Boy Frame Memorial Lecture, Henry Ford Hospital, Detroit, 2005
Campbell Lecture in Nutrition Education, University of Guelph, Guelph, Ontario, 2006

## PUBLICATIONS

## ABSTRACTS

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A-8. Heaney RP. Radiocalcium metabolism in human disuse osteoporosis. J Lab Clin Med 56:825, 1960.

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A-10. Skillman TG, Heaney RP. Endogenous intestinal calcium secretion. J Lab Clin Med 60:1018-1019, 1962.
A-11. Heaney RP, Skillman TG. Normal calcium kinetics: Application of a newly derived composite reference standard. J Lab Clin Med 62:882, 1963.
A-12. Heaney RP, Kramar P. Mechanism of development of osteoporosis in the immobilized rabbit calcaneus (trueta preparation). Proc of Orthop Res Society, January, 1965.
A-13. Sullivan JF, Heaney RP. Zinc 65 metabolism in patients with cirrhosis. J Lab Clin Med 38:76, 1965.

## A-14. Heaney RP. Kinetic studies in human osteoporosis. J Bone Jt Surg

A-15. Heaney RP, Skillman TG. Calcium metabolism in normal human pregnancy. J Clin Invest 49:41a, 1970.
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A-18. Heaney RP, Recker RR, Saville PD. Calcium balance and calcium requirements in middleaged women. Clin Res 22:649A, 1974.

A-19. Heaney RP, Recker RR. Estrogen effects on bone remodeling at menopause. Clin Res 23:535A, 1975.
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A-23. Heaney RP, Recker RR. The anion effect during calcium supplementation. Clin Res 32:520A, April 1984.
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A-25. Weaver CM, Heaney RP, Martin BR. Oxalic acid inhibits calcium absorption. Proc Soc Exp Biol Med 46(3):631, 1987.
A-26. Heaney RP. Qualitative factors in osteoporotic fracture: The state of the question. International Symposium on Osteoporosis Abstracts, p. 24, 1987.
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fracture due to misclassification bias. Am J Epidemiol, 1995.
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## Exhibit 2

|  | Page | Study/ Article | Journal |
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| 1 | LL650- <br> LL652 | "Title 21-FOOD <br> AND DRUGS: <br> CHAPTER 1- <br> FOOD AND DRUG <br> ADMINISTRATIO <br> N, DEPARTMENT <br> OF HEALTH AND <br> HUMAN <br> SERVICES- <br> CONTINUED: <br> PART 101 FOOD <br> LABELING-Table |  |
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m, 1995\end{array}\right] .\)| LL667- |
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| 6 | LL676- <br> LL679 | Peripheral <br> computed <br> tomography (pQCT) <br> detected short-term <br> effect of AAACa <br> (heated oyster shell <br> with HAI) | Journal of <br> Bone and <br> Mineral <br> Metabolis <br> m, 2000 |
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| 7 | LL680- <br> LL684. | "Osteoporosis: <br> Past, Present and <br> Future." T. Fujita. | Osteoporo <br> sis <br> Internatio <br> nal, 1997 |



| 9 | $\begin{array}{\|l\|l} \hline \text { LL690- } \\ \text { LL695. } \end{array}$ | "Effects of Active <br> Amino Acid <br> Calcium: Its <br> Bioavailability on <br> Intestinal <br> Absorption, <br> Osteoporosis and <br> Removal of <br> Plutonium in <br> Animals." Satoshi <br> Fukada. | Journal of <br> Bone and <br> Mineral <br> Metabolis <br> m, 1998 |
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| 10 | $\begin{aligned} & \hline \text { LL696- } \\ & \text { LL703. } \end{aligned}$ | "Osteoporosis in Asia." Takuo Fujita, M.D. | Calcium Research Institute, Kishiwada , Japan |
| 11 | $\begin{aligned} & \hline \text { LL704- } \\ & \text { LL707. } \end{aligned}$ | "Calcium supplementation and parathyroid hormone." Shigeki Ohgitani, Yoshio Fujii, and Takuo Fujita. | Journal of <br> Bone and <br> Mineral <br> Metabolis <br> m. (1998) |


| 12 | LL708- <br> 731. | "Calcium and <br> Osteoporosis." <br> Takuo Fujita. | Calcium <br> Research <br> Institute, <br> Osaka, <br> Japan |
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| 13 |  | LL732 <br> "Calcium <br> supplementation <br> reduces vertebral <br> bone loss in per <br> menopausal women: <br> a controlled trial in <br> 248 women <br> between 46 and 55 <br> years of age." P.J. <br> Elders, et al. | Abstract <br> from the <br> Clinical <br> Indocrino <br> Metab. |
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| 19 | LL765 "Please Note: <br> Several Other <br> Studies on AAACa <br> Calcium <br> (AdvaCAL) <br> Published in <br> Japanese are <br> available but not <br> included in the <br> binder. They are <br> available upon <br> request." <br> 21 (2001) |  |  |
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|  |  | LL766- | LAn interview with <br> Takuo Fujita, M.D." |


| 22 | LL793 | "" 'AdvaCAL ${ }^{\text {TM }}$ is the \#1 Bone Building Calcium. Period.' " Bone and Joint Health . | Bone and <br> Joint <br> Health |
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| 42 | $\begin{aligned} & \text { LL845- } \\ & \text { LL846 } \end{aligned}$ | "Serum parathyroid hormone in healthy Japanese women in relation to serum 25 hydroxyvitamin D." K. Nakamura, et, al. | Internatio <br> nal <br> Journal of <br> Vitamin <br> Nutr <br> Research. <br> 2000. |
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| 44 | LL849- <br> LL850 | "Dietary calcium <br> and vitamin D <br> intake in elderly <br> women: effect on <br> serum parathyroid <br> hormone and <br> vitamin D <br> metabolites." H.K. <br> Kinyamu, et, al. | The <br> American <br> Journal of <br> Clinical <br> Nutrition. <br> $1998 .$. |
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| 52 | LL869- <br> LL870 | "CALCIUM + <br> VITAMIN D <br> SHOWN <br> EFFECTIVE IN <br> PREVENTING HPP <br> FRACTURES IN <br> THE ELDERLY <br> (70+ YEARS)." <br> Advertisement. |  |
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| 54 | LL872- <br> LL873 | "Acute changes in <br> serum calcium and <br> parathyroid <br> hormone circulating <br> levels induced by <br> the oral intake of <br> five currently <br> available calcium <br> salts in healthy male <br> volunteers." R. <br> Deroisy, M., et, al. | Clinical <br> Rheumato <br> logy. <br> 1997. |
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| 62 |  | LL882 <br> Calcium <br> supplementation <br> and bone loss in <br> middle-aged <br> women." E.L. Smith <br> et al. | Am J Clin <br> Nutr, <br> 1989. |
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| 118 | LL964 | $\begin{aligned} & \text { "Safety of some } \\ & \text { calcium } \\ & \text { supplements } \\ & \text { questioned." SH } \\ & \text { Whiting. } \end{aligned}$ | Nutr Rev., $1994 .$ |
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| 131 | LL992 | "Clinical trial of microcrystalline hydroxyapatite compound ('Ossopan') in the prevention of osteoporosis due to corticosteroid therapy." A Pines et al. | See Row 104. |
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| 132 | LL993 | "Calcium absorption and achlorhydria." RR Recker. The New England Journal of Medicine. 1985. | $\begin{aligned} & \text { See Row } \\ & 105 . \end{aligned}$ |


| 133 | LL994- <br> LL998 | "Acute <br> Biochemical <br> Variations <br> Induced by Four <br> Different Calcium <br> Salts in Healthy <br> Male Volunteers.". <br> J.Y. Reginster, D. <br> Denis, V. Bartsch, <br> R. Deroisy, B. <br> Zegels, and P. <br> Franchimont. <br> Osteoporosis <br> International. <br> 1993. <br> 106. |
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| 135 | LL1001 | "The acute <br> biochemical <br> effects of four <br> proprietary <br> calcium <br> preparations." $\mathbb{R}$ <br> Reid, BA <br> Schooler, SF <br> Hannan, and HK <br> Ibbertson. Aust N <br> ZJMed. 1986. | See Row <br> 110. |
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| 136 | LL1002 | "Long-term <br> effects of calcium <br> supplementation <br> on bone loss and <br> fractures in <br> postmenopausal <br> women: a <br> randomized <br> controlled trial." <br> RR Reid, RW <br> Ames, MC Evans, <br> GD Gamble, and <br> SJ Sharpe. <br> American Journal <br> of Medicine. <br> 1995. | See Row |
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| 137 | LL1003- <br> LL1004 | 'Long-term <br> effects of calcium <br> supplementation <br> on serum <br> parathyroid <br> hormone level, <br> bone turnover, <br> and bone loss in <br> elderly women." <br> B.L. Riggs, W.M. <br> O'Fallon, J. <br> Muhs, M.K. <br> O'Connor, R. <br> Kumar, and LJ <br> Melton 3'. <br> Journal of Bone <br> and Mineral <br> Research. 1998. | See Row <br> 112. |
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| 138 | LL1005 | "Meta-analysis of <br> calcium <br> bioavailability: a <br> comparison of <br> calcium citrate <br> with calcium <br> carbonate." K <br> Sakhaee, T <br> Bhuket, B Adams- <br> Huet, and DS <br> Rao. American J <br> Ther. 1999. | See Row <br> 113. |
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| :--- | :--- | :--- | :--- |
| 143 |  | LL1019 | Illegible copy of <br> $2 " x 2 " t e x t ~ b o x . ~$ |


| 144 | LL1020- <br> LL1026 | "Dose <br> Dependency of <br> Calcium <br> Absorption: A <br> Comparison of <br> Calcium <br> Carbonate and <br> Calcium Citrate." <br> Jean A. Harvey et <br> al. | Journal <br> of Bone <br> and <br> Mineral <br> Research, <br> 1988 |
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| 145 | 1050 | LL1027- | USPTO Information |


| 146 | LL1051 | "Calcium <br> Bioavailability from Heated Oyster ShellSeaweed Calcium (Active Absorbable Algae Calcium) as Assessed by Urinary Calcium Excretion." T. Fujita, et al. | J Bone <br> Miner <br> Metab, <br> 1996. |
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| 147 | LL1051-2 | "Calcium Paradox <br> Disease: Calcium <br> Deficiency <br> Prompting <br> Secondary <br> Hyperparathyroidis m and Cellular Calcium Overload." <br> T. Fujita and G. <br> Palmieri. | $\begin{aligned} & \hline \text { J Bone } \\ & \text { Miner } \\ & \text { Metab, } \\ & 2000 . \end{aligned}$ |


| 148 | LL1052 | "Calcium <br> Supplement and Parathyroid <br> Hormone." S. <br> Ohgitani, et al. | $\begin{aligned} & \text { J Bone } \\ & \text { Miner } \\ & \text { Metab., } \\ & 1998 . \end{aligned}$ |
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| 149 | LL1052-3 | "Degenerative Joint <br> Disease: An <br> Example of Calcium Paradox." T. Fujita. | $\begin{aligned} & \text { J Bone } \\ & \text { Miner } \\ & \text { Metab., } \\ & 1998 . \end{aligned}$ |
| 150 | LL1053 | "Heated Oyster Shell with Algae Ingredient (AAACa) Decreases Urinary Oxalate Excretion." S. Ohgitani and T. Fujita. | no journal given; study conducted at Calcium Research Instit. In Japan. |


| 151 | LL1053-4 | Increase of <br> Intestinal Calcium <br> Absorption and <br> Bone Mineral <br> Density by Heated <br> Algal-Ingredient <br> (HAD) in Rats." T. <br> Fujita, et al. | no journal <br> given; <br> study <br> conducted <br> at Institute <br> of Science <br> and <br> Technolog <br> y in <br> Japan. |
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| 152 | LL1054 | "Calcium Paradox <br> Disease: Calcium <br> Deficiency <br> Prompting <br> Secondary <br> Hyperparathyroidis <br> m and Cellular <br> Calcium Overload." <br> T. Fujita and G. <br> Palmieri. | n/a |



| 155 | LL1055-6 | "A Three-Year Comparative Trial in Osteoporosis Treatment: Effect of Combined Alfacalcidol and Elcatonin." T. Fujita, et al. | J Bone <br> Miner <br> Metab., <br> 1997. |
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| 156 | LL1056 | "Effects of Amino Acid Calcium: Its Bioavailability on Intestinal Absorption, Osteoporosis and Removal of Plutonium in Animals." S. Fukuda. | $\begin{aligned} & \hline \text { J Bone } \\ & \text { Miner } \\ & \text { Met., } \\ & 1998 . \end{aligned}$ |


| 157 | LL1056 | "Overnight <br> Suppression of <br> Parathyroid <br> Hormone and Bone <br> Resorption Markers <br> By Active <br> Absorbable Algae <br> Calcium. A Double- <br> Blind Crossover <br> Study." T. Fujita, et <br> al. | Calcif <br> Tissue |
| :--- | :--- | :--- | :--- |
| Int., 1997. |  |  |  |$|$

## Exhibit 3



25 October 1999

Andrew J. Larie
President

## LaneLabs

110 Commerce Drive
Allendale, New Jersey 07401
Dear Mr. Lane:
You asked that I provide you with an evaluation of the AAACa product and its associated research. You also asked several questions in your cover letter. Here is my best attempt to provide you with the answers you requested. I have tried to be as restrained in my approach as I could, in order not to run your bill up unduly, So, please let me know if $I$ can help further.
In addition to responding specifically to your questions and to the materials supplied, I have taken the liberty of preparing a brief background treatment of some of the issues dealing with bone remodeling and with the effects of calcium supplementation thereon. I bellieve you will need this in order to have the context in which claims' about "building bone" can be understood or make sense or be defended.
In my treatment I have confined myself pretty much to the blological science. I am certain you recognize that successful marketing of a product is based on something more than the luvolved science. Acquiring rights to the product is a business decision, and whether you should do that or not is not within my arena of competence to advise.
You raised two points in your letter that I think I can deal best with here, before launching into a more detailed review of the Fujix material.

- The fact that these studies were done in Japanese individuals would not, in my opinion, constitute a barrier to their acceptance by the scientific community or to their generalizability to other races.
- What would be a barrier to general scientific acceptance is the fact that the studies have all been performed by an individual who has a commercial interest in the product. This is not, for a moment, to suggest dishonesty, just the absence of full scientific objectivity.

Andrew J. Lane

25 October 1999
Page 2

- You mention that the elderly showed an increase in BMD, and characterized them as a "tough" population in which to show such a change. Actually the opposite is the case. They are the easiest group in which to show that kind of change. This is partly because of the phenomenon known as the remodeling transient, which I desculbe in greater detail in the attachment, and partly because the calcium requirement actually rises in the elderly, so that the intake of an elderly person tends to be moxe deficient than that of younger individuals, and hence the response to supplementation is relatively greater.
Sincerely yours,

Robert P. Heaney, M.D.
Enclosures

## BONE "BUILDING" AND THE REMODELING TRANSIENT

## Bane Remodeling

Bone is continuously remodeling itself, and the effects of calcium (and pharmacotherapy) on the remodeling process produce changes in BMD that rneed to be distinguished from changes in stoady state bone balance.
In the remodeling process, microscopic units of bone are actually eaten away (the process known as "bone resorption"), and then later replaced with fresth new bone, (the process known as "bone formation"). The balance between the two processes is what determines whether we are gaining bone, losing bone, or maintaining bone, tncidentally, all bone loss and gain come about in this way, Bone mass changes only through shifts in remodeling balance.
Remodeling removes damaged portions of the structure and helps keep our bones resilient. A principal determinant of the total quantity of bone remodeling in the akeleton as a whole is the amount of parathyroid homone (PTH) being procuced and circulating in the blood. PTH secretion, in turn, is inversely proportional to effective calojurn intake. The site of action of PTH is both at the initiation of the remodeling process, and on the resorption step. PTH is often thought of as a bone weakening hormone, because it does stimulate bone breakdown. When calolum intake is not adequate to offset daily losses, it is PTH that causes the remodeling imbalance that loads to bone loss (thereby making calcium available for other body needs). But whether bone mass is reduced or not is a function of the calcium intake. At high calcium intakes, PTH actually leads to an increase in bone in certain skeletal regions.
At the remodeling site the processes of resorption and formation are always asynohronous, l.e., the demolition and repair processes cannot go on simultaneously, Rather, as with remodelling of a building, the demolition precedes the repair. While this is inevitably true locally, when averaged over the skeleton as a whole, there should be about as much repair as demolition occurning on any given day. When, in the steady state, there is an excess of demolition, then more bone is being broken down than is being replaced and bone mass is deoreasing. Conversely, as during growth, when formation exceeds resorption, bone is being "built", Both of these statements apply to the steady state situation, and it is to this steady state that we would normally apply the term "bone building". This emphasis is important because, when remodeling is altered, it takes some time before a new steady state is reached. The time required, at a local site, to complete the remodeling process, from beginning of destruction to the conclusion of repair, is typically on the order of 3-6 months in healthy young adults, and six months to two years in older individuals.

Perhaps a helpful way to think about the consequences of this asynchrony is to compare our skeletons to a large hotel. Let's say that you have 500 rooms. After the hotel has been in use for some time, there will be rooms that will have to be taken out of service because they need repair. Also, at the same time you, as manager, must deal with decisions about whether to expand by edding on another wing, or to constrict, by converting space to some other use. Repair is analogous to remodeling of the akeleton, and expansion and conversion are analogous to bone building and bone loss, respectively.
Now, if your clientele is typically dominated by rock groups and their followers, you will constantly be sustaining a lot of damage that will require a lot of repair. Thus, on any given night perhaps 50 of your rooms will be unavailable for rent, l.e., you can only use 450 rooms, because 50 are being repainted, recarpeted, or their plumbing repaired. Assume that you, as manager, make a decision to change your clientele, and not to aocept reservations from these destructive groups, and to focus instead on marketing to temperance groups and oonventions of church women. In the weeks and months following this policy decision, you will experience some of the old rooms coming back into service as you complete their repairs, but you will be taking a lot fewer rooms out of service. Thus, instead of 450 rooms available on a glven night under the old reservations policy, you will experience an increase to $460,470,480$, etc., until you reach some minimum level of repair below which you oan never drop. Have you "built" more hatel? Well, you certainly have more rooms to tent than you did a few weoks ago, and you generate more revenue. So in one sense you have more hotel, but in another sense what you have is simply more usable hotel.
Precisely the same is true of the skeleton. Having more usable skeleton is just as good for skeletal strength as hieving more rooms to rent is good for your hotel business. But it is not the same thing as building more bont or more hotel, in the strict sense of the term.

## The Bone Remodeling Transient

In the hotel business the critical factor is the change in clientele, while in the skeleton the critical factor is the change in the level of PTH. The elderly typically have both less bone and substantially elevated PTH levels. Thus they have fewer "rooms" to start with and more rooms out of service because of high remodeling. In certain skeletal regions, that can mean that as much as $10-20$ percent of the skeleton is currently being remodeled, and is not, therefore, structurally useful now. Why is remodeling rate so bigh? One major reason is effective calcium deficiency - or perhaps more precisely - decreased ability with advancing age to adapt to an insufficient intake. Axy factor that reduces that remodeling rate (such as supplemental calcium) will give you an immediate gain in usable skeleton. The phenomenon is oalled a "remodeling transient". The reason why it is called "transient" will be evident in what follows.

Incidentally, this transient is the basis for my statement in the cover letter to the effect that an increase in BMD following calcium is easier to see in the elderly than at any other time of life. The elderly are simply remodeling more of their skeleton, and that remodeling is suppressible when one gives extra calcium. These responses are a part of the reason why science now believes the eldexly are often calojum deficiont.
But a problema remains as to how one interprets the data from clinical studies in which bone mass is measured before starting calcium supplementation, and then again after some period of treatment. I am enclosing a figure adapted from a chapter I wrote on this topic, which shows schematioally the time course of bone mineral density under conditions of no calcium supplementation and then with supplementation in two hypothetical groups of patients. You will notice from the figure that there is an immediate rise in the treated group, lasting about a year, following which thete is a leveling off of bone mineral density and then a gradual decline with time. The tise is the transient. You will notice also that, in the untreated group, there is a steady decline with time. Further, you will notice, in this hypothetical case, that the rates of dedine in the two groups after the remodeling transient is over are different, with the calcium-supplemented individuals losing at a slower rate than the unsupplemented. Finally, you will notice that if you make only two measuroments, one before and the other after some period of treatment, what appeats to happen will be different depending upon the time of your second measurement. With a short interval, there is a very substantial inorease in measurable bone (l.e, BMD), but as the interval stretches out, the supplementation appears to be less and less effeotive. But those different appearances are simply an artifact of when we choose to measure, Clearly the calcium supplementation is having a positive effect throughout. The calciumsupplemented individual, at all time points, has more usable bone (and therefore more bone strength) than the unsupplemented individual. Morcover, after the transient, the rate of bone loss is reduced in the calciumsupplemented group, So, for both reasons, the supplemented individual enjoys a benefit of the extra calcium.
But a semantic question arises as to whether this is "building bone". To paraphrase President Clinton: What do you mean by the word "build"?



## CALCIUM, CALCIUM SALTS, and AAACa

Calctum, of course, exists in nature in combination with a variety of anions, The principal calcium supplement salts in use in the U.S. are calcium cerbonate, the various calcium phosphates, and a variety of calolum salts of organie acids, such as the citrate, malate, glubionate, lectate, etc. Generally the anion makes relatively little difference, and despite wide variation in aqueous solubility (spanning 4-5 otders of magnitudel), most of the caldium salts are absorbed at very nearly the same efficiency (generally in the range of $25-35$ percent at ingested loads in the range of 300 mg ). Furthermore, with some relatively minor exceptions, calcium is dissociated from its anion and loses any connection with it in the process of being absorbed. Again, with some minor exceptions, the principal significance of the anion relates to issues such as tablet bulk, palatability, cost, and other such considerations.
It is true that complex salts such as caloium citrate malate are somewhat more absorbable than calcium carbonate, which in turn is more absorbable than cealcium phosphate, etc. But the differences are realiy quite small, and the advantages associated with one or another form come more from the marketing edge they confer on their products than from a consideration of nutritional economios. (Thus, taking a couple extra Tums a week will obliterate any advantage that CCM may have over calclum carbonate, at far less cost than getting all one's supplemental calcium from CCM.)
While many manufacturers would like to think that they have a special ingredient which somehow enhances the absorbability or the effectiveness of the calcium in their product, there is no general scientific acceptance that suoh special ingredients exist. That is not to say that some might not be discovered, just that norre is recognized today.
Having sald that, I must also note that the Fujix AAACa is chemically and pharmaceutically different from other calclum supplement formulations in that its principal salt appears to be calcium hydroxide, and it contains the so-called heated algal ingredient (HAI). To my knowledge, calcium hydroxide is not used in any other product, and its absorbability has never been directly tested using generally accepted methods, What we know about its absorbability, as well as of the effect of the HAI, comes to us solely from the work of the Fujix Company and of Dr. Fujita himself. It is concelvable that calcium hydroxide may be substantially more absorbable than the more usual salts, or that HAI enharces absorbability (particularly to individuals with gastric aoid, although gastric acid is not actualiy necessary for calclum absorption, despite popular lore to the contrary). The papers you supplied do provide some information on both points and I shall evaluate that evidence below.
Finally, calclum absorbability differences, to the extent any exist, may have a greater marketing benefit than a nutritional benefit. This is because
unabsorbed calcium in the food residue produces useful and important detoxification effects in the intestine in its own right. From purely nutritional considerations, one should be interested not in enhancing calclum absorbability, but in increasing caloium intake. Dr. Fujita to the contrary notwithstanding, the problem with today's diets is not that the calcium is pootly absorbable but that the calcium intake is so much lower than would have been the case under primitive conditions.

## INTERVIEW WITE TAKUO FUJITA

Dr. Fufita is a senior clinical bone invostigator in Japan, is well known internationally, and has contributed usefully to the advance of the field. As is the case for any human being, he has viewpoints and paradigms within which he interprets data, and these will not always be shared universally among his peers. Thus the comments that I shall offer bolow are not so muoh criticism (although in several instances I believe the statements attributed to him are factually incorreot), as they are an attempt to give LaneLabs the sense that there may be other views on some of these topios.
To begin with, absorption of calcium carbonate is not "very poor" even in the total absence of stomech acid. This is simply on error of fact Calciuma carbonate is actually slightly more absorbable than the calcium of milk, as shown in literally dozens of expeniments using radloactive calciummabeled calcium sources. And milk calcium absorbability reflects the absorbability of mixed food diet calcium generally, (Milk is, in effect, the gold standard here.) Second, to the extent that AAACa can be equated with calcium hydroxide, it is not true to say that calcium hydroxide is "highly" soluble. It is certalnly more soluble than calclum carbonate (see axy handbook of chemistry and physios), but when placed in water it forms a milky particulate suspension, rather than going totally into solution. When 500 mg of calcium as the hydroxide is placed into 100 mL of hot water, less than $10 \%$ will go into solution.
Similarly, it is not true that the phosphorus of milk reduces the absorbability of its calcium. Over very broad ranges of CaiP ratio (from 0.2 to 2.0 ), phosphorus intake hes no influence whatsoever on calcium absorption. This has been demonstrated by multiple investigators, using a variety of methods. The best explanation that I know of for the seeming paradox of what happens in the test tube and what happens in the intestine is that phosphorus is fairly readily absorbed ( $60-80$ percent) so that residual phosphorus in food is not present in sufficient quantity to complex the calcium in the intestinal contents. (There is also the fact that no theory exists for the highly concentrated mixture that is the chyme, and extrapolations from dilute solution chemistry to this milieu can be very misleading.)
The foregoing comments on Dr. Fujita's statements about other sources of calclum are not particularly relevant to the issue of whether AAACa could be a good source of calcium, or could be a useful product for a company to market. Dr. Fujita's statements reflect, instead, the theoretical (rather than evidence-based) type of argumentation that is commonly employed to convince someone that a partioular product might be better than another. But suoh arguments never carry any weight by themselves; they must be buttressed by facts. I believe that Dr. Fujita is substantially in error on the
foregoing points, but I suspect it is simply a matter of uncritically thinking about some of these issues because of an understandable desire to promote his own brainchild. As 1 say, while AAACa could be better than some other formas, in terms of absorbability, it doesn't have to be highly absorbable to be good in its own right, and it would not detract from AAACa to say that other forms of calcium are good, too. As implied in the brief treatment enclosed on "Calcium, Calcium Sources, and AAACa", as far as the body and the bones are concerned, all calcium looks pretty much alike. As stated there, calcium loses its association with whatever may have accompanied it in the tablet as soon as it is absorbed (if not already in the chyme). Outside of the halls of the supplement manufacturers, in the general nutition and bone biologic communities, calcium is calcium. Period. (The scientific community may be wrong. So I don't state this so much as fact, as to tell you what the prevailing view is.)

## EVALUATION OF SCIENTIFIC PAPERS AND DOCUMENTATION PROVIDED BY FUJX

## Compositlonal Data and Patent

Ass stated in the patent and inferred in several other pieces of documentation, the calcium form in AAACa is principally calcium hydroxide, though statements are made to the effect that there is some calcium oxide, as well. The popular name for calodum oxide is lime, which is caustic, and one presumes that the manufacturers would not have created an oral dosage form that contained a caustio compound. Indeed, the composition table supplied by Fujlx is not compatible with the presence of any calcium oxide at all. As noted in earlier corregpondence, the composition table cannot be reconciled with all of the caloium being present in the form of calcium hydroxide, either, and What the remaining calcium species may be, or whether the analysis is incorrect, is uncertaln.

The current product also contains $25 \%$ citric acid by weight. When added to an aqueous medium about one-fourth of AAACA will conyert to caloium citrate.
In several places, both in the patent document and in earlier papers by Dr. Fujita, $A A A C a$ is characterizod as "aotive amino acia" calcium, However, the composition table states that the amino acid level is too low to be quantified. Furthermore, the method of calcining the oyster shell powder would be expected to destroy any organic material. The patent states that the absence of oxygen in the calcining process somehow preserves the amino acids, but no evidence is presented to support that claim, and it is hard to imagine that such amino acids, even if present, could be exerting any biological effect if they are at levels too low to be detected. Furthermore, the patent states that the amino acids are somehow "layered" between tiers of calcium oxide crystals, but again no evidence is provided to support that statement.
Finally one notes in passing how flexible and fluid the name has been over the post few years. At one time the product was called HOSS - "heated oyster shell seaweed calcium"; then it became OSE - "oyster shell electrolysate"; then AAACa - "active amino acid calcium"; then that acronym was retained but shifted to mean "ective absorbable algal calcium"; and now it is just "active absorbable calcium" or "AAACa". The shift away from the term "active amino acid" in the title suggests to me that the authors have abandoned their earlier contention in this regard. Also, one must wonder whether the product itself, or just its name, has changed over these years. This is not just nit-picking. If the product has changed in daportant ways, muoh of the documentation provided with respect to earlier formulations must be judged irrelevant for the current AAACa with HAI.

The current process seems to include the admixture of a heated algal component (HAI). I am not experienced in reading patents, but it would seem that U.S. Patent $5,296,246,000$ does not cover the KAII component of the current product. This distinction may be important because some of the documentation provided (see below) suggests that HAI may have a benefit in its own right. If so, HAI could be added to any calcium source to produce that benefit.

Finally, it may be noted that, on page 3 of the patent, under the heading "Background of the Invention" there are many serious misstatements of fact. Specifically, paragraphs four through seven axe substantially or totally incorreot.

## Evaluation of Publlshed Scientific Papera

N.B.i I have focused my review matnly on the papers that have been published, rather than on the poster presentations and manuscripts provided. I have also checked References 1 to 3 of the Fukuda papar.

- JBMM 1997 - This paper shows that AAACa produces a bone bemefit. No comparative data are provided for other calcium sources. The production of a bone benefit is presumptive evidence that the produot is absorbable.
- Min Elect Met 1995 - See below.
- CTI 1996 - These are the same patients as described in the foregoing publication. The method of analysis of the data employed by the authors is incorrect, statistically. Furthermore, it is hard to evaluate the data provided, inasmuch as the numbers of individuals at each sampling point decline with follow-up, and the within-individual data are not supplied. In any oase, there appears to be little apparent difference between plaia calclum carbonate and AAACa in this study.
- OI 1997 - This paper is simply a comment. It contains no experimental data.
- CTI 1997 - This paper presents a comparison of two dosing regimens of AAACa. There is no comparison with other calcium sources. Although absorption efficienoy is not directly measured, the data show that the product is absorbable. The suppression of PTH and the other changes described have also been shown by other investigators for other forms of calcium.
- JBMM 1998 - Fukuda - This paper presents the only comparative data for AAACa and another calcium source (calecium carbonate). It is, however, performed in animals. Figures 1 and 2 show clearly higher blood levels of calcium with AAACA than with calcium carbonate in both rats and dogs, but the details of these infusion experiments are not given. Indeed, the experiments described in the Methods section seem
not to be related to the data of these two figures at all. The sizes and phyalcal form of the infused loads are not given, and the degree of elevation of blood calcium produced would indicate either huge loads, or major mucosal damage associated with the load. To give some idea of the magnitude of the increase, the degree of hypercalcemia produced in the rats with AAACa, if it had occurred in humans, could well be fatal. The breaking force and histomorphometrio data in Figures 3 and 4 do not compare AAACa with calcium carbonate.
- Although not provided in sufficient detall for any kind of proper evaluation, the poster presentations suggest activity of the heated algal ingredient ( HAD ). The Abstract states that, in a four-way trial in humans, AACa without HAI was not different from calcium oarbonate or placebo.
- Bone Miner 1990 - This is a study of a single product (OSE presumably later called AACa), showing a small effeot at one site (but not others) in elderly women. If OSE is similar to AAACA, this could be taken as evidence of absorbability, but the paper prowides no comparative data.
- NRIZ 1997 - As far as I can tell from the English language Abstract (the original paper is in Japanese) this is a poorly designed experiment which shows, for the most part, comparability between AAACa and milk calcium, though it does appear that the calcium loads were different for the two sources. The only point of difference between the two products was in PTH level, and this could mean greater absorbability for AAACa, but there are other intergretations just as plausible, and more information would be needed before one could be certain of the meaning of this work.
- Ref. 1 from the Fukuda paper (Bone Miner 1988 - not supplied by Dr. Fujita) actually contains the only comparative human data that are interpretable with respect to $A A A C a$ and calciun carbonate. In four patients with hypocaicemia due to hypoparathyroidism, OSE Ca increased serum calcium to a greater extent than calcium carbonate; moreover, there was a much greater rise in urine calcium with OSE Ca, These date indicate that OSE Ca is absorbable, and in this case, more so than a calcium carbonate preparation (type unspectifed). Given the other clinical data, I believe absorbability for OSE Ca (if it is the same as HOSS, AACa, and AAACa) can be considered to be very probable. Relative absorbability (vis-à-vis other salts) is less clear.


## Comment

The product, $A A A C a$, is a oalcium source of uncertain composition, but presumably principally calclum hydroxide (and partly calcium citrate when in aqueous suspension). Calcium hydroxide is a calcium source new to human
supplementation, and its properties have not been well characterized, Calcium citrate is well studied, and by itself is no more absorbable than calclum carbonate. From the data provided, it would appear that AAACa is absorbable, but no proper absorbability tests have been performed, and no convincing comparative data have been brought forth that would support olaims of superiority. The heated algal ingredient (HAI) is apparently new to the product, and fragmentary data are provided suggesting that it may exert some calcium-enhancing activity in its right. These need to be confirmed.
As noted earlier, superior absorbability is not necessarily nutritionally adyantageous; however, it could confer a marketing advantage on a product. The data that have been provided to me would not constitute convincing evidence of such superiority, and if LaneLabs were to decide to utilize this product, some test establishing superior absorbability would seem to be mandatory. The best such test would not be feasible for this product, since the test would require the introduction of an isotopic tracer into the product, and given the product's physical characteristics, that would not be possible. Hence it would be necessary to use less precise methods, such as companative hypercalcemia or hypercalciuria produced by equivalont caloium loads ingested in two or more chemical forms. Such tests are feasible and could be done for relatively modest cost. Advertising that claimed superiority without more convincing evidence than is now provided by Fujix, would invite challenge by either the FTC or the Better Business Bureau (cf. the action by SmithKline Beecham against Mission Pharmacal, with regard to the latter's unsupportable olaims of superior absorbability for calcium citrate).
If LaneLabs is interested in pursuing this venture further, it may be that the company could split the cost of the comparative absorbability testing with Fujix. My own laboratory could perform the indicated testa for you, or if you wished a further degree of independence, could help you design the needed experiment and place it with another investigator.

## Exhibit 4



Dr. I. William Lane

# "AdvaCAL" is the \#1 Bone Building Calcium. Period." 

## Stronger Bones = Fewer Fractures.



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"The National Osteoporosis Foundation reports that most Americans are calcium deficient. Osteoporosis has become a national epidemic. Osteoporosis is reversible if you take the right type of calcium. I recommend AdvaCAL to men and women of all ages. The pills are small, easy-to-swallow and amazingly effective. It's the only calcium I've seen that has been shown over and over to build bone density."
—Dr. I. William Lane


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| te and Asian women rea | ce their osteoporosis risk in later life. |  |  | Exhibit 4 | Age |

## Exhibit 5

# Heated Oyster Shell-Seaweed Calcium (AAA Ca) on Ostepporosis 

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#### Abstract

Abstrace. A tandomized. prospective, jouble-blind test was carried out to comparc thic cffects of heared oyster sheil-seavveed calcium (AAA Ca), calcium carbonate, and placebo in 58 elderly, hospitalizcd womicn with the mean age of 80 divided inro three groups. Group A received 900 my/day Ca as AAA Ca. Group B $900 \mathrm{mg} / \mathrm{day} \mathrm{Ca}$ as $\mathrm{CaCO}_{3}$, and Group C placebo besides rcgular hospital dier containing approximately 600 mg Ca/day for 24 months. From the 25 th io the 30 th month, all grougs werc given AAA Ca. Lumbar spine and radial bone mineral densicy (BMD) were measured at 3-month intervals. Uninary Ca/Ci and serurn alkaline phosphatase, intact and midportion serum paraciyroid hormonc (PTH), and calcitonin were also measured ar intervals. From the oth to the 24 th month of the study, the ratio or lumbar spine $\mathbb{B M D}$ ( $\mathrm{L}_{2}-\mathrm{L}_{1}$, by DPK. Lunar) to einc basal pretest value was consistendy and significandy higher in Group A shan Group C but not higher in Group $\mathbb{B}$ than in Group C. PTH, measured 12 monthe after the becginning of the study, was lower in Group $A$ ghan in Group $C$. bur no significant difference was tound between Groups $B$ and $C$. At 3 monchs after the placebo was switched to AAA Ca in Group C , serum PTH was significantly decreased from the level during placebo supplement. Morming urime Ci/CT decreased in Groups $A$ after 18 months and in $B$ after 12 months, bur nor in C . Serum althaine phosphatase decreased in Group A significandy compared with Group $C$, but not in Group B. AAA Ca appears to be effective for increasing BMD in cideriy subjects.


KSey words: Hcaiced oystcr shell seaweed Ca - Osteoporosis - Parathyroid hormone - Allcaline phosphatase Uninary $\mathrm{Ca} / \mathrm{C}$. .

Oyster shell heated in yacuo (AA Ca) was reported to be absorbed from the intestine more efficienuly than calcium carbonate [1, 2]. It also increases radiai bone mineral density ( 3 MD) (measured by single photon absorptiometry) and spinal crabecular BMD (measured by quanritative compured tomography $[3,4]$ ). Since heared oyster shell-seaweed calcium (AAA Ca, Fujir, Tokyo) was found in be even more efficienty absorbed than oyster shell heated in vacuo in intact and parathyroidectomized rats [5], it appears worthwhile to compare the ciffect of this new calcium prep-

[^0]aration on bone density with that of widely used calcium cartonate in elderiy subjects with reduced intestinal Ca absorption. A randomized prospective, and double-blind controlled study was therefore underaken on a group of elderly hospitalized subjects so evaluate the effect of AAA Ca on BMD and paramesers of calcium metabolism in comparison with calcium carbonate and placebo.

## Suinjects and Methods

Fify-eighr chronically hospitalized elderly patients ayed 65-96 (mean $\pm$ SD: $80 \pm 6$ ) widhout diseases primarily affecing the skeleral system were randomly divided inio chree groups of similas age and lumbar spinal bone density. Each patient was assigned to one of the three groups according to the date of admission: Group A 20 subjects aged $40 \pm 6$ (mean $\pm$ SD), Group B, 18 subjects aged $83 \pm 4$, and Group C, 20 subjects uged $79=9$. Excluded were 24 pationss with severe compression fracture-compression or fracures-or marked osienphyle formation in $\mathrm{L}_{2}-\mathrm{L}_{4}$ as well as severe calcificalion of abdominal aoma intericring with accurate measurement. Degree of acriviry was ciassified into three grades: 3 for freely walking around without assislance, 2 for walking around with assistance, and 1 for being confined to wheclehair or bed. Group A cousisted of $35 \%$ with activity level 3, $35 \%$ with 2 , and $30 \%$ with 1 (mean $2.05 \pm 0.80$ 5D); Group B 33. 28, and $39 \%$ (mean $1.94 \pm 0.84$ ); and Group C 20, 55 , and $25 \%(1.95 \pm 0.66)$. respecively. Mean serum $25(\mathrm{OH}$ ) vitamin D levels were $11.3 \approx$ 3.$\}_{r} 10.7 \pm 2.1$, and $10.1 \pm 12 \mathrm{ng} / \mathrm{nll}$ in Croups $A, B$, and $C$. respectively, each group exhibixing miid vitamin D deficiency expected in elderly hospiealized paciencs. The changes of lumbur $B M D$ in the same supplement group with differem degree of acavity were generally indisanguishable.

All parients wers unded regular hospital diel containing approximarely 600 mg calciumiday. In addition. six of cither of the three kindis of indistinguishable capsules were given daily in threc divided doses after cach meal. Ite three lands of sapsules consained 150 mg Ca as AAA Ca for Group A. 150 mg Ca as CaCO (precipitated calcium carbonate, Japanese Pharmacopeia) and for Group B. a piaccbo coneaining no Ca for Group C . The three doses provided 900 mg/day $C a$ supplement for Groups $A$ and $B$ and nothing for Group $C$. At the end of the 24 -month period, supplements in Groups B and C were swichicd to AAA Ca, and Group A was kept on the same supplement to continuc the obscrvarion for 6 more months.

Lumbar spine BMD ( $L_{2}$, ) and midradial BMD at the junction of the middle and diseal onc-third site was measured with dual energy \%-ray absorpriomerry (DXA) by DPX (Junar) before the beginning of the trial and every 3 months for 1 year and every 6 monehs after that. Coefficient of variation was $1.8 \%$ for lumbar BMD and $2.8 \%$ for midradial BMD on 10 repeated measurements of the same subject on differemt days. Midradial BMD was not

Table an. Changes of lumbar bone mineral dencity

| Group | A | C | C |
| :--- | :--- | :--- | :--- |
| Betore | $0.625 \pm 0.134$ | $0.615 \pm 0.134$ | $0.633 \pm 0.176$ |
|  | $(19)$ | $(17)$ | $(20)$ |
| 3 M | $0.637 \pm 0.133$ | $0.608 \pm 0.145$ | $0.617 \pm 0.167$ |
|  | $(17)$ | $(17)$ | $(20)$ |
| 6 M | $0.569 \pm 0.139$ | $0.596 \pm 0.149$ | $0.616 \pm 0.200$ |
|  | $(15)$ | $(13)$ | $(17)$ |
| 9 M | $0.652 \pm 0.139$ | $0.581 \pm 0.127$ | $0.620 \pm 0.191$ |
|  | $(14)$ | $(12)$ | $(11)$ |
| 12 M | $0.659 \pm 0.137$ | $0.599 \pm 0.116$ | $0.634 \pm 0.107$ |
|  | $(13)$ | $(10)$ | $(6)$ |
| 18 M | $0.656 \pm 0.094$ | $0.643 \pm 0.100$ | $0.609 \pm 0.149$ |
|  | $(5)$ | $(7)$ | $(5)$ |
| 24 M | $0.674 \pm 0.119$ | $0.624 \pm 0.136$ | $0.633 \pm 0.182$ |
|  | $(5)$ | $(6)$ | $(7)$ |
| 30 M | $0.722 \pm 0.037$ | $0.665 \pm 0.078$ | $0.691 \pm 0.151$ |
|  | $(4)$ | $(4)$ | $(6)$ |

$M=$ month
Changes of lumbar spine $B M D, L_{2}-L_{4} G / \mathrm{cm}_{2}$ (mean $+S D$ ) hrough the eser period in Group A supplemented with 900 mg/day calcium as AAA Ca, Group B supplemented with $900 \mathrm{mg} /$ day calcium as CaCO , and Group C not supplemented with calcium, up to the 24 ch month, when $900 \mathrm{mg} / \mathrm{day}$ calcium as AAA Ca replaced $\mathrm{CaCO}_{3}$ in $\mathrm{Group}_{\mathrm{B}}$ and placebo in group C . In the lower pari of the Table, the courses of changes or each value expressed as ravios to the individuai busal value before the begianing of the study or rales of chunges arc showm. The number of samples for each sel is given in parenthesis
measured at the 30 ch month, since a change or software made it impossible to compare the newly oblained values with the previous ones.

Second morming urine samples werc obtained every month and the mean over each 6 -mimonth period was used to represent this period. Blood samples were obnined for serum aikaline phosphatase measurement every monch, and the mean over each 6 -month period was used to represent the period. Blowid samples for PTH and calcitonin measuremenr were obrained in the midij]5 of the srudy period 12 months after the beginning of the study when each group was on its respective suppiement, and at 27 months ather the beginning of the study when all groups were receiving AAA Ca-for 27 months in Group $A$ and 3 months in Groups $B$ and $C$. Scrum intact ETH was measured by immunoradiometric assay (Nichols), midportion PTH by fadioimmunoassay using the antiberly raised by Slazopolsky ot al in the chicken (Yamasa), and scrum calcionin by radioimmunuassay.

Dara were sratistically analyzed by analygis of variance (ANOVA) using Sarview 4.02 system by Fisher's PSLD, Sheffe. and Bonferroni-Dumn merhod. Fisher's PSLD was used for multiple comparison with a consiant varisnce, Sheffe's method was used to compensate for different sample sizes arnong the groups, and Bonfertumi-Duns's method for correction of the risk level. The results of measurement were expressed in absolute values and also as ratios to each individual basal value at the beginning of the suruy or the rates of changes, vo corrcet for the variability of dara possibly because of the high age of the test subjects. Consequently. the lower half of Tables 11004 expressing the mean and SD of the ratios to each basal valuc or tates of changes were nor calculared from the mean and SD of absolute values shown in the upper halk of the respective Tables. The number of samples incvitably decreased progreasively in each group because of the long study period and the high age of the lest subjects. FIH and CT valucs were compared on the same subjiccts during the use of different supplements in each group and after switching the supplement to AAA Ca in all the groups.

The study was approved by the Insticutional tucview Board of Karsumgi Hospizal. Tiformed consent was obtained from cach patient who participared in the study.

Taible 1b. Changes of the fatios of fumbar spine $\operatorname{BMD}$ to the basal value

| $3 \mathrm{M} / \mathrm{B}$ | $\begin{aligned} & 100.4 \div 3.5 \\ & (17) \end{aligned}$ | $\begin{aligned} & 98.5 \pm 3.7 \\ & (17) \end{aligned}$ | $\begin{aligned} & 98.4 \pm 4.6 \\ & (20) \end{aligned}$ |
| :---: | :---: | :---: | :---: |
| $6 \mathrm{~m} / \mathrm{B}$ | $\begin{aligned} & 101 . \mathrm{J} \pm 4.2^{n} \\ & (15) \end{aligned}$ | $\begin{aligned} & 97.1 \pm 4.3 \\ & (13) \end{aligned}$ | $97.2 \pm 6.7^{9}$ <br> (17) |
| 9 MB | $\begin{aligned} & 100.6 \pm 42^{D} \\ & (14) \end{aligned}$ | $\begin{aligned} & 97.8 \pm 4.0 \\ & (12) \end{aligned}$ | $94.7 \pm 6.5^{h}$ <br> (Ii) |
| 12MB | $\begin{aligned} & 101.9 \pm 40^{\circ} \\ & (13) \end{aligned}$ | $\begin{aligned} & 9 R .0 \pm 53 \\ & (10) \end{aligned}$ | $96.3 \pm 7.1^{c}$ (6) |
| 18MB | $\begin{aligned} & 103.3 \pm 3.8^{14} \\ & (5) \end{aligned}$ | $\begin{aligned} & 98.9 \pm 1.9 \\ & (7) \end{aligned}$ | $94.3 \pm 7.5^{4}$ <br> (5) |
| 24M/6 | $\begin{aligned} & 103.2 \pm 3.8 \\ & (5) \end{aligned}$ | $100.6 \pm 6.2$ | $96.6 \pm 4=$ <br> ( 7 ) |
| $30 \mathrm{M} / \mathrm{B}$ | $101.8 \pm 5.5$ <br> (4) | $\begin{aligned} & 100.7 \pm 9.6 \\ & (4) \end{aligned}$ | $99.1 \pm 5.4$ <br> (6) |

Significant at $P<0.05$ by ANOVA by Fisher's PSLD
$2 p=0.0460$ adso significant by Bonferoni-Dunn method
${ }^{n} P=0.0050$ also significant by Shefic and Bonfertoni-Dunan methods
$\stackrel{P}{P}=0.0354: d p=0.0083 ;{ }^{\mathrm{s} p}=0.0434$

## Reruits

Lumbar spine $B M D\left(L_{2}-\mathbb{L}_{4}\right)$ decreased in Group $C$ to 96.6 $\pm 4.5 \%$ of the basai vaiue at the 24 th month, but increased to $103.2 \pm 3.8 \%$ in Group $A$. The ratios to the basal value were significandy higher in Group A than in Group C between the sih and $24 t h$ months, as shown in Table 1. No significant difierence, however, was found berween Group $B$ and Group $C$. In the 30 th monch of the study, 6 monen's after switching to AAA Ca in all groups, the value in Group $C$ increased and no significant difference was any longer found among the three groups. Radial BMTD was preserved in Group A but tended to fall in Groups B and C (Table 2).

Morning urinary calcium/crearinine ralio decreased from the basai kevel significantly in Group $A$ after 18 months and in Group B after 12 months, but not as remarkably in Group C (Table 3). The ratio to the basal level, however, signifisantly declined only in Group A, from $1-7 \mathrm{MB}$ to 19. $24 \mathrm{M} / \mathrm{B}$ and $25-30 \mathrm{M} / \mathrm{B}$, after an inimal nise. Urinary $\mathrm{Ca} / \mathrm{C}$ ? seemed to fall in Groups $B$ and $C$ in the $25-30$ h months after $\mathrm{CaCO}_{3}$ or placebo was switched to AAA Cin, but this was not statistically significame. Serum alkaline phosphatase decreased in Group A more remarkably than in C. As shown in Table 4, the ratio to the basol value was significantiy lower in $A$ ghan in $C$ ar $1-6$ and 19-24 months. These difterences again disappeared after 6 monehs of AAA Ca ingestion in each group.

Although PTH was not measured as the beginning of the sudy, both intsci and midporion PTH was significantly lower, and caicitonin bigher. in Group A bur not in Group $B$ than in Group $C$ at the 12 bh month from the beginning of the sudy. After AAA Ca was given in all the groups, intact PTH in Group C showed a significan fall with disappearance of the significant difference from Group $A$, as shown in Tabice 5.

## Discussion

Oyster sheil heated in vacuo was prepared by heating powdered oyster sheils at reduced oxygen concentration at approximately $960^{\circ} \mathrm{C}$. Though the original oyster shell mainily

Teplife 2. Changes of radial BMD

| Group | A |  | 8 |  | C |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Before | $\begin{aligned} & 0.456 \pm 0.088 \\ & \text { (18) } \end{aligned}$ |  | $\begin{aligned} & 0.437 \pm 0.087 \\ & \text { (18) } \end{aligned}$ |  | $\begin{aligned} & 0.501 \pm 0.130 \\ & (19) \end{aligned}$ |  |
| $3{ }^{\text {崖 }}$ | $\begin{aligned} & 0.449 \pm 0.092 \\ & (18) \end{aligned}$ |  | $\begin{aligned} & 0.429 \pm 0.085 \\ & (18) \end{aligned}$ |  | $\begin{aligned} & 0.498 \pm 0.122 \\ & (18) \end{aligned}$ |  |
| 6 M | $\begin{aligned} & 0.444 \pm 0.116 \\ & (13) \end{aligned}$ |  | $\begin{aligned} & 0.449 \mp 0.078 \\ & (11) \end{aligned}$ |  | $\begin{aligned} & 0.493 \pm 0.119 \\ & (16) \end{aligned}$ |  |
| 9M | $\begin{aligned} & 0.441 \pm 0.093 \\ & (14) \end{aligned}$ |  | $\begin{aligned} & 0.445 \pm 0.120 \\ & (13) \end{aligned}$ |  | $0.504 \pm 0.151$ |  |
| 12M | $\begin{aligned} & 0.439 \pm 0.089 \\ & (13) \end{aligned}$ |  | $\begin{aligned} & 0.453 \pm 0.106 \\ & (10) \end{aligned}$ |  | $0.463 \pm 0.122$ <br> (b) |  |
| 18M | ${ }^{0.432 \pm 0.114}$ |  | $0.477 \pm 0.098$(B) |  | $\begin{aligned} & 0.438 \pm 0.122 \\ & (5) \end{aligned}$ |  |
| 24M | (6) $0.476 \pm 0.0051$ |  | $0.448 \pm 0.023$ |  | $0.473 \pm 0.040$ |  |
| $3 \mathrm{~N} / \mathrm{B}$ | $\begin{aligned} & 98.3 \\ & (18) \end{aligned}$ | $\pm 4.4$ | $\begin{aligned} & 98.6 \\ & (18) \end{aligned}$ | $\pm 7.7$ | 97.4 <br> (19) | $\pm 5.9$ |
| 6M/8 | $\begin{aligned} & 98.1 \\ & (13) \end{aligned}$ | $\pm 7.4$ | 98.9 (11) | $\pm 7.3$ | (14.9 | $\pm 5.8$ |
| 9M8 | $\begin{aligned} & 98.5 \\ & (14) \end{aligned}$ | $\pm 6.6$ | $\begin{aligned} & 97.0 \\ & (13) \end{aligned}$ | $\pm 9.7$ | $96.5$ <br> (y) | $\pm 4.8$ |
| 12M/B | 99.4 (13) | $\pm 3.3$ | 97.7 (10) | $\pm 8.2$ | (87.1 | $\pm 6.3$ |
| 18M/B | $\begin{aligned} & 100.3 \\ & (9) \end{aligned}$ | \$4.6 | 98.0 <br> (8) | \$9.3 | 97.3 <br> (5) | $\pm 6.5$ |
| 24NLB | $\begin{aligned} & 100.5 \\ & (6) \end{aligned}$ |  | $98.8$ <br> (3) | $\pm 3.0$ | 97.0 <br> (5) | $\pm 3.3$ |

Changes of the radial BMD measured by DPK ar the junction of distal and middic onc-mikrd (RBMD g/cm $\mathrm{cm}^{2} \pm \mathrm{SD}$ ) in Group A supplemerred with 900 me calcium as AAA Ca. Group B supplemented with 900 mg calcium as $\mathrm{CaCO}_{3}$, and Group C supple. menred with placebo comisining zo calcium up to the 24th month. In the sccond part of the Table, changes of the values are expressed as percencages of the baseline value prior to the best. Change of the software precluder comparabie measurement at the 30th month. Numbers in parenthesis indicate sample numbers.
contains calciun carbonale, the oyster shell heared in vacuo showed a characreristic lamellar crystalline strucrure distinct from cither calcium carbonate or calcium oride, its final ouidation produce It may represent calcium oxide in a peculiar spacial arrangement, maintaining the ready solubility and biosvailability of calcium oxide without its imirability [1].

This uyster shell heated in yacuo was found to contain a trace amount of amino acids despite the exposure to a high iemperanure of $900^{\circ} \mathrm{C}: 0.012 \mathrm{mg} / 10 \mathrm{~g}$ serine, $0.008 \mathrm{mg} / 10 \mathrm{~g}$ glycine, $0.018 \mathrm{mg} / 10 \mathrm{~g}$ groline, and $0.017 \mathrm{mg} / 10 \mathrm{~g}$ leucine. AAA Ca was prepared by adding scesweed preparation similarly heated at $900^{\circ} \mathrm{C}$ containing the same order of quancities of tisuidine, Eyrosime, and valine in addition 10 oyster shell heared in vacuo.

In the present swody, AAA Ca was found to increase lumbar spine BMD signiñicantly better than the placebo, but the effect of the same amount of Ca supplied as $\mathrm{CaCO}_{3}$ was not significant over placebo. Midradial BMD showed a similar but less pronounced change, mantenance at che initial level in Croup A, and a moild decrease in Group $\mathbb{B}$ and further decrease in Group C . Morning urine $\mathrm{Ca} / \mathrm{Cr}$ mainly reflects bone resorplion. since the conuribution or̃ the absorbed calcium is expected to be minimal at inis time. In these eiderly subjects, factors such as degree of exercise, changes of nuid intale, and decline of senal function may

Page 3

Terate 3a. Changes of winary $\mathrm{Ca} / \mathrm{Cr}$ ratio

| Groups | A | $B$ | $C$ |
| :--- | :--- | :--- | :--- |
| Sefore | $0.364 \pm 0.229$ | $0.399 \pm 0.251$ | $0.328 \pm 0.449$ |
|  | $(19)$ | $(18)$ | $(19)$ |
| $1-6 \mathrm{M}$ | $0.309 \pm 0.162$ | $0.32 \pm \pm 0.140$ | $0.297 \pm 0.213$ |
|  | $(18)$ | $(17)$ | $(16)$ |
| $7-12 \mathrm{M}$ | $0.322 \pm 0.170$ | $0.285 \pm 0.129^{\mathrm{B}}$ | $0.254 \pm 0.190$ |
|  | $(16)$ | $(15)$ | $(14)$ |
| $13-18 \mathrm{M}$ | $0.236 \pm 0.159$ | $0.223 \pm 0.127^{\mathrm{h}}$ | $0.242 \pm 0.072$ |
|  | $(13)$ | $(11)$ | $(8)$ |
| $19-24 \mathrm{M}$ | $0.177 \pm 0.093^{\mathrm{c}}$ | $0.216 \pm 0.087^{\mathrm{C}}$ | $0.197 \pm 0.105$ |
|  | $(12)$ | $(9)$ | $(8)$ |
| $25-30 \mathrm{M}$ | $0.173 \pm 0.115^{\mathrm{C}}$ | $0.179 \pm 0.087^{\mathrm{r}}$ | $0.174 \pm 0.0083$ |
|  | $(10)$ | $(9)$ | $(4)$ |

Course of changes of moming urinary calcium/creatinine ralio in Group A supplemented with $900 \mathrm{mg} / \mathrm{day}$ calcium as AAA Ca, Group $B$ suppiemenied with 900 mgday calcium as $\mathrm{CaCO}_{3}$ and Group $C$ given placebo nor concaining calcium for 24 monkhs. After 24 monchs. $\mathrm{CaCO}_{3}$ and placebo in Groups B and C were replaced with 900 mg/day calcium as AAA Ca. Mean and SD of 6 gmonthly data were used to ecprescne inc oucrall trend during this perioui In the second part of the Table, each valuc expressed as percencages of the basal pre-test value was similarly suminarized. Numbers in parenchesis indicatc sample numbers
ANOVA by Fisher's PSLD
Difiference from the basal precest value was significant at ${ }^{s} P=$
 $=0.0013$ also signifucent by Eonfernoni-Dunn method

Table 3 b . Changes of the raios to the basal value of urinary $\mathrm{Ca} / \mathrm{Cl}_{7}$

| Groups | A | $B$ | $c$ |
| :---: | :---: | :---: | :---: |
| 1-6M81 | $\begin{aligned} & 1.055 \pm 0.552 \\ & (18)^{\mathrm{ab}} \end{aligned}$ | $0.936 \pm 0.429$ (17) | $\begin{aligned} & 2.135 \pm 0.425 \\ & (16) \end{aligned}$ |
| 7-12M | $\begin{aligned} & 1.098 \pm 0.499 \\ & (16) \end{aligned}$ | $\begin{aligned} & 0.972 \pm 0.663 \\ & (15) \end{aligned}$ | $\begin{aligned} & 0.928 \pm 0.420 \\ & (14) \end{aligned}$ |
| 13-188 | $\begin{aligned} & 0.755 \pm 0.292 \\ & (13) \end{aligned}$ | $\begin{aligned} & 0.954 \pm 0.462 \\ & (\mathbb{1}) \end{aligned}$ | $1.044 \pm 0.524$ (8) |
| 19-24M | $\begin{aligned} & 0.710 \pm 0.456 \\ & (12)^{4} \end{aligned}$ | $0.738 \pm 0.399$ <br> (9) | $0.868 \pm 0.421$ <br> (b) |
| 25-30M | $\begin{aligned} & 0.722 \pm 0.485 \\ & (10)^{4} \end{aligned}$ | $\begin{aligned} & 0.606 \pm 0.327 \\ & \text { (9) } \end{aligned}$ | $0.734 \pm 0.524$ <br> (9) |

$\mathrm{B}=$ Significandly different by ANOVA with Fisher's PSLD ${ }^{\circ} P=$ 0.0417 and ${ }^{\text {s }} P=0.0373$. respectively
influence urinary excretion of salcium and creatinine, so that the inicrprctation of these data requires additional cauzion. Serum alkaline phosphatase reflects bonc turnover and is known to rise in osteoporosis. Decrease of chese paramerers may therefore indicate inhibition of bone resorpion which may be pronounced in elderly subjects with low cuilcium incake and poor intestinal absorption of calcium due to vilamin $\mathbb{D}$ deficiency. Serum imtaci and midportion PTH indicacing the degree of calicium deficiency and predicting the degree of bone resorption rended to be lower on supplementalion with AAA Ca, with a significant fall in Group C after switching from placebo to AAA Ca, suggesting PTH suppression and decreased bone resorption in response to effective calcium supplement. Improvement of lumbar BMD on switching so AAA Ca from placebo, along with à frall of serum PTH in Group $C$, appears to confirm the effect

Exhibit 5

Tabie 4. Changes of serum alkaine phosphatase

| Groups | A | B | C |
| :---: | :---: | :---: | :---: |
| Qefore | $9.1 \pm 3.9$ <br> (19) | $\begin{aligned} & 8.9 \pm 2.7 \\ & (16) \end{aligned}$ | $\frac{8.2 \pm 2.6}{(17)}$ |
| 1-5M | $\begin{aligned} & 8.2 \pm 3.4 \\ & (19) \end{aligned}$ | $\frac{8.2}{(16)} \pm 2.5$ | $\begin{gathered} 8.6 \pm 2.9 \\ (17) \end{gathered}$ |
| 7-12m | $\begin{aligned} & \text { 8.6 } \pm 3.5 \\ & (13) \end{aligned}$ | $7.2 \pm 2.0$ <br> (10) | ${ }^{8.1 \pm} 1.9$ |
| 13-1898 | $\begin{gathered} 7.8 \pm 2.8 \\ (13) \end{gathered}$ | $\begin{aligned} & 7.2 \pm 2.2 \\ & (11) \end{aligned}$ | $8.3 \pm 2.0$ <br> (线) |
| 19-24M | $7.1 \pm 2.7$ <br> (10) | $\begin{aligned} & 6.9 \pm 1.9 \\ & (11) \end{aligned}$ | $8.4 \pm 1.3$ <br> (6) |
| 25-301 | $\begin{aligned} & 6.3 \pm 1.5 \\ & (9) \end{aligned}$ | $6.5 \pm 1.4$ <br> (8) | $7.9 \pm 2.5$ <br> (6) |
| 1-6M/8 | $\begin{aligned} & 91.9 \pm 19.6 * \\ & (19) \end{aligned}$ | $\begin{aligned} & 93.7 \pm 19.9 \\ & (16) \end{aligned}$ | $\begin{aligned} & 105.7 \pm 16.4^{2} \\ & (17) \end{aligned}$ |
| 7-12M/B | $\begin{aligned} & 98.5 \pm 42.3 \\ & (13) \end{aligned}$ | $98.2+26.2$ <br> (10) | $108.6 \pm 27.0$ <br> (7) |
| 13-18M | $\begin{aligned} & 89.6 \pm 27.8 \\ & (13) \end{aligned}$ | $\begin{aligned} & 91.3 \pm 28.1 \\ & (11) \end{aligned}$ | $108.4 \pm 34.2$ <br> (8) |
| 19-24M | $79.1 \pm 22.2^{\circ}$ <br> (10) | $\begin{aligned} & 89.2 \pm 30.3 \\ & (11) \end{aligned}$ | $109.8 \pm 29.6^{6}$ <br> (6) |
| 25-30M | $\begin{aligned} & 84.7 \pm 3.52 \\ & (9) \end{aligned}$ | $93.0 \pm 22.2$ <br> (8) | $90.2 \pm 32.4$ <br> (6) |

Course of alkaline phosphatase (King-Akmstrong units, mean $\pm$ SD) in Group A supplemented with 900 mg/day calcium as AAA Ca. Group B supplemented with $200 \mathrm{mg} / \mathrm{day}$ calcium as $\mathrm{CaCo}_{37}$ and Gioup C nor suppiementen with caicium, ap to 24 months. Atter this period, all ihree groups wcre supplemented with $9(0)$ myday galcium with AAA Ca. In the second part of the Tablc. each value expressed as percentages of the individual basal pretest vaiue is suminarized Numbert in parenthesis indicates sample numbers.
Signiticant difference between ${ }^{\mathrm{ap}}=0.313 ;{ }^{0} p=0.0402$ by ANOVA with Fisher's PSLD

Taible s. Cbanges of serum parahyroid hormone and caicironin

| Groups | A |  | 8 | $C$ |
| :---: | :---: | :---: | :---: | :---: |
| IPTH (test) | $\begin{aligned} & 26 \pm \\ & (7) \end{aligned}$ | $9{ }^{\circ}$ | $38 \pm 13$ <br> (6) | $47 \pm 11^{20}$ <br> (8) |
| iPTH (atter) | $\frac{22}{(7)}$ | 7 | $\begin{aligned} & 33 \pm 17 \\ & (6) \end{aligned}$ | $24 \pm 10^{\circ}$ <br> (8) |
| mPTH (best) | $487 \pm$ <br> (7) |  | $755 \pm 200^{\circ}$ <br> (6) | $\begin{aligned} & 2 \geq 5 \pm 268^{1} \\ & (8) \end{aligned}$ |
| MPTH (after) | $\begin{aligned} & 353 \pm 1 \\ & (7) \end{aligned}$ |  | $622 \pm 133^{e}$ <br> (6) | $634 \pm 235^{5}$ <br> (B) |
| CT (test) | $27 \pm$ | $5^{8}$ | $\underset{(6)}{23 \pm} 5$ | $18 \pm \quad 55$ <br> (6) |
| CT (atter) | $21 \pm$ | 4 | $\frac{20 \pm}{(6)}$ | $\begin{aligned} & 18 \pm 4 \\ & (6) \end{aligned}$ |

Senm intact pararhymid hornone (IPTH), midportion parathyroid hormone ( mPTH ), and calcionin (CT) in PD/mi $\pm \mathrm{SD}$. During the first 24 munths, Group A was supplemented with $900 \mathrm{mg} / \mathrm{day}$ calcium as AAA Ca, Group B with 900 mge calcium as $\mathrm{CaCO}_{3}$ and Group C with piscebo. After this period, all Groups were supplemented with 900 mg calcium as ANA Ca as in Croup A. Values at the 12th monih of the study (test) and 6 monibs after the swiech of the supplemenes (after) arc shown. Numbers in parenthesis indicare sample numbers.
Signiticant differences by Fisher's PSLD
${ }^{3} P=0.0024 ;{ }^{\circ} P=0.0060 ;{ }^{4} P=0.0122 ;{ }^{4} P=0.0015 ;{ }^{\circ} P=$ $0.0122:{ }^{5} P=0.0071$; ${ }^{B} P=0.0022$

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of AAA Ca Calcium carbonate also appeared to decrease urinary calcium excrecion, but the ratio to the basal level failed to change significanily from the level in the firsi 6 months, unlike AAA Ca.

The reason for the good bioavailability of AAA Ca suggested in the present study remains io be elucidated. Though cursain amino acids are known to increasc intestinal absorpcion of calcium, the amount of amino acids found in AAA Ca was much less than the level at which any such action of amino acids is expected [ 6,7$]$. Since serum $25(\mathrm{OH})$-vitamin D values were low in each group and the degree of activity was also similar, the property of calcium supplement seems to be dominant

Caicium supplement increased bone density or inhibited the age-bound bone loss [ $8-13]$, bur also failed to prevent postmenopausal bone loss complerely [14, 15]. DawsonHughes [16] pointed out the nced for supplement of about 1000 mg or more of calcium to see a positive effect and also showed that the effect depended on the years after menopause. Cumming [17] reviewed trials of calcium supplement, pointing out better effects of calcium supplement in premenopausal women with low calcium intake. Since estrogen itself favors calcium absorption. the presence of estrogen may provide a better environment for the cffect of calcium supplementation. Recently, Elders et al. [18] showed a positive effect of long-term calcium supplement in perimenopausal women. However, none of these studies so far reported concentrated on clderly women as in the present sudy. presumably decause of difficulies accompanying such studies on subjects who are exremely age. In patients in this age range, especially those in the insuiutions, some vitamin $D$ deficicncy is inesitable and the incrinsic bioavailability of the calcium preparation appears to be crucial to achieving a positive effect.

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Exhibit 5

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## Exhibit 6

# Reappraisal of Katsuragi Calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAACa) on vertebral deformity and fracture 

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#### Abstract

A prospective, double-blind, placebo-controlled study of the effect of supplementation with $900 \mathrm{mg} /$ day of calcium, as active absorbable algal caicium (AAA Ca) or calcium carbonate ( $\mathrm{CaCO}_{3}$ ), on lumbar bone mineral density (BMD) carried out in elderly inpatients with osteoporosis at Katsuragi Hospital was re-evaluated in terms of the effects on vertebral fracture and spondylotic deformity. In addition to the already reported increase in lumbar BMD, AAA. Ca was found to inhibit new occurrence of vertebral fracture. Intraindividual variations in $\mathrm{L}_{1}-\mathrm{L}_{4}$ BMD (expressed by the coefficient of variation, indicating the degree of spondylatic deformity, were also inhibited significantly in the group supplemented with AAA Ca (group A), but not in group B (supplemented with $\mathrm{CaCO}_{3}$ ), from the level in the placebosupplement group (group C) after 18 months of supplementation. According to whole-body dual-energy X-ray absorptiometry (DXA.) results in the first and second year of the study, whole body mass, lean content, and mineral content, expressed as a percentage of whole body mass, stayed unchanged, while increase of fat content was significantly inhibited in group $A$, but not in group $B$, from the level in group C. As to the regional distribution of bone mineral content, the second year/first year value for head bone mineral content was significantly decreased with AA.A supplementation compared with placebo, but no significant difference was found between $\mathrm{CaCO}_{3}$ and placebo supplementation. Changes in mineral distribution in the arms, trunk, and legs showed no significant differences among the three groups. In addition to increasing BMD and preventing fracture, AAA Ca , but not $\mathrm{CaCO}_{3}$, appears to inhibit the occurrence of spondylotic deformity and to decrease body fat content.


Key words osteoporosis • spondylotic deformity • fat mass - active absorbable algal calcium (AAA Ca) - dual-energy X-ray absorptiometry (DXA)

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## Introduction

A prospective, randomized, double-blind, placebocontrolled study was carried out to determine the effect of active absorbable algal calcium (AAA Ca) on osteoporosis in three groups of elderly patients hospitalized at Katsuragi Hospital, Osaka, Japan (Katsuragi Calcium Study) [1]. The three groups received daily supplementation with: (1) 900 mg calcium as AAA Ca (group A), (2) 900 mg calcium as calcium carbonate $\left(\mathrm{CaCO}_{3}\right.$, group B$)$, and (3) starch placebo containing no calcium (group C). The supplement was given daily in six capsules (indistinguishable among groups) over a period of 2 years. Lumbar bone mineral density (BMD), measured by dual-energy absoptiometry (DXA) in the anterior-posterior direction was significantly higher in group A (supplemented with AAA. Ca) than in the placebo-supplemented group $C$, whereas no significant difference was found between group $B$ (supplemented with $\mathrm{CaCO}_{3}$ ) and group C .
In the present study, the data for DXA of the lumbar spine were re-analyzed to calculate the intra-individual standard deviation (SD) and coefficient of variation (CV; SD divided by mean) of $\mathrm{L}_{1}-\mathrm{L}_{4}$ BMD to assess the development of spondylotic changes [2-5]. Lateral spine X-ray films taken before and after the study in groups $\mathrm{A}, \mathrm{B}$, and C were evaluated, and the intraindividual $C V$ of the projected area of the $L_{1}-L_{4}$ vertebral bodies was calculated to detect new occurrence of fracture. Whole body DXA was performed in the first and second year of the study to follow changes in whole body mineral content and other parameters.

The Katsuragi Calcium Study was conducted in 58 hospitalized elderly women randomly divided into three groups of similar age, lumbar BMD, and grade of daily
physical activity. All patients were receiving a regular hospital diet containing approximately 600 mg Ca daily. Group A, consisting of 20 subjects with a mean age of $80 \pm 6$ years (mean $\pm \mathrm{SD}$ ) was given $900 \mathrm{mg} /$ day Ca supplement as AAA Ca; group B, consisting of 18 subjects aged $83 \pm 6$ years, was given $900 \mathrm{mg} /$ day Ca supplement as precipitated $\mathrm{CaCO}_{3}$ (Japanese Pharmacopeia), and group $C$, consisting of 20 subjects aged $79 \pm 9$ years, was given placebo containing no Ca . Each supplement was contained in six indistinguishable capsules, two to be taken after each meal daily, over a period of 2 years, under a strict double-blind principle.
In addition to the mean $\mathrm{L}_{1}-\mathrm{L}_{4} \mathrm{BMD}$, measured by DXA in the anterior-posterior direction (LBMD), intra-individual variation of $\mathrm{L}_{1}-\mathrm{L}_{4}$ BMD was evaluated by calculating the $S D$ and coefficient of variation (CV; SD divided by the mean $\mathrm{L}_{1}-\mathrm{L}_{4} \mathrm{BMD}$ ) at $3,6,9$, 12,18 , and 24 months after the beginning of the study, using a Lunar DPX instrument (Madison, WI, USA) [2-5]. Subjects with a marked loss of vertebral height within $\mathrm{L}_{1}-\mathrm{L}_{4}$, suggesting compression fracture, were excluded prior to entry.
Vertebral fracture was assessed before and after the trial, based on lateral X-ray films of the thoracic and lumbar spine, in six, seven, and six subjects in groups A, $B$, and $C$, respectively. New appearance in a decrease in either the middle or anterior vertebral height by $20 \%$ or more, compared to the posterior height of the same vertebra, or the one immediately adjacent, was defined as the occurrence of vertebral fracture. The CV of the projected area of $L_{1}-L_{4}$ vertebral bodies was also calculated to detect vertebral compression fracture expressing itself as an increase in the intra-individual variation of the projected areas.
Whole body DXA was performed in the first and second year of the study ( 6 and 18 months after the beginning of the study) to measure the whole body mass, lean content expressed as a percentage of the whole body mass; mineral content expressed as a percentage of the whole body mass; and fat content expressed as a percentage of the whole body mass. Distribution of regional mineral content in the head, arms, trunk, and legs was also calculated, as a percentage of the whole body mineral content [6]. Because no whole body measurement was performed prior to the beginning of the study, the value for second year/first year (\%) was used as an index of the change.
Statistical analysis, consisting of multiple comparison with analysis of variance and Fisher's protected least significant difference (PLSD) test and the $\chi^{2}$ test was carried out on Statview 5.0 (Abacus Concepts, Berkley, CA, USA).
Informed consent, given by the patients or their families, was obtained, and the study was approved by the Institutional Review Board of Katsuragi Hospital.

## Results

As shown in Fig. 1, the mean $\mathrm{L}_{1}-\mathrm{L}_{4}$-BMD started to rise 6 months after the beginning of the study in group A (supplemented with AAA Ca), suggesting restoration of the decreased bone mass, leading to a significant difference from group $C$ (given placebo) throughout the rest of the study period, as already reported, whereas group B (supplemented with $\mathrm{CaCO}_{3}$ ) showed no significant difference from group $C$ (supplemented with placebo) [1]. Intra-individual variation of $\mathrm{L}_{4}-\mathrm{L}_{4}$ BMD, expressed as CV (shown in Fig. 2), on the other hand, was significantly suppressed in group A (supplemented with AAA Ca) from the level in the placebosupplemented group $C$ after 18 months, suggesting inhibition by AAA Ca supplementation, of the development of spondylotic changes. Group $B$ (supplemented with $\mathrm{CaCO}_{3}$ ) did not exhibit a significant difference from either group A or group C in mean BMD or intraindividual variation. The SD of $\mathrm{L}_{1}-\mathrm{L}_{4} \mathrm{BMD}$ showed no significant difference among the three groups, as shown in Fig. 3.

In the six subjects in group A (supplemented with AAA Ca) for whom lateral spine X -ray films were examined for the occurrence of new fracture, no new vertebral fracture occurred during the study period of 2 years, whereas, in two of the seven subjects in group $B$


Fig. 1. Mean lumbar bone mineral density ( $B M D ; \mathrm{L}_{4}-\mathrm{L}_{4}$ ), expressed as a percentage of the basal value on the ordinate and time in months on the abscissa, in the Katsuragi Calcium Study, as already reported. Group A, supplemented with active absorbable algal calcium (AAA Ca) is shown by squares; group B , supplemented with $\mathrm{CaCO}_{3}$, as circles; and group C , supplemented with placebo, as triangles. Increase of the mean lumbar BMD was significantly greater in group $A$ than in group C after six months. No significant difference was found between group $B$ and group $C$ or between group $B$ and group A. Multiple comparison was done by analysis of variance and Fisher's PLSD. Mean $\pm$ SEM


Fig．2．Coefficient of variation（CV）of $\mathrm{L}_{1}-\mathrm{L}_{4} \mathrm{BMD}$ ，expressed as a percentage of the basal value on the ordinate and time in months on the abscissa，in the Katsuragi Calcium Study． Group A，supplemented with AAA Ca，is shown by squares； group $B$ ，supplemented with $\mathrm{CaCO}_{3}$ ，as circles；and group C ， supplemented with placebo，as triangles．After 18 months， changes in the CV of $\mathrm{L}_{1}-\mathrm{L}_{4} \mathrm{BMD}$ ，expressing the degree of spondylotic deformity over the basal level，were significantly greater in group $C$ than in group $A$ ，suggesting effective sup－ pression of spondylotic deformity by AAA Ca．No significant difference was found between group B and group C or be－ tween group B and group A．Multiple comparison was done by analysis of variance and Fisher＇s PLSD．Mean $\pm$ SEM


Fig．3．Intra－individual SD of $\mathrm{L}_{4}-\mathrm{L}_{4} \mathrm{BMD}$ ，expressed as a percentage of the basal value on the ordinate and time in months on the abscissa，in the Katsuragi Calcium Study． Group A，supplemented with AAA．Ca，is shown by squares； group B ，supplemented with $\mathrm{CaCO}_{3}$ ，as circles；and group C ， supplemented with placebo，as triangles．No significant differ－ ence was found among the three groups at any time．Multiple comparifongeas done by analysis of variance and Fisher＇s PLSD．Mean $\pm$ SEM


Fig．4．Frequency of occurrence of new fractures during the 2－ year study period in the Katsuragi Calcium Study．Open bar represents group A，supplemented with AȦA Ca；shadowed bar，group B ，supplemented with $\mathrm{CaCO}_{3}$ ，and closed bar， group C，supplemented with placebo．According to the $\chi^{2}$ test， the frequency of fractures was significantly greater in group C （250 patients／1000 years）than in group A（0 patient／1000 years；$P<0.05$ ），but no significant difference（ $n s$ ）was found between group B（ 143 patients／ 1000 years）and group $C$
（supplemented with $\mathrm{CaCO}_{3}$ ）and three of the six sub－ jects in group $C$（supplemented with placebo）similarly studied，a vertebral fracture was sustained during the same period，making the yearly incidence of new frac－ ture per 1000 subjects 0 for group A， 143 for group B， and 250 for group $C$ ，the difference between groups $A$ and C being significant，by the $\chi^{2}$ test，at $P<0.05$ ，as shown in Fig．4．No significant difference was found between group B （supplemented with $\mathrm{CaCO}_{3}$ ）and group C（supplemented with placebo）．The CV of the projected area of the vertebral bodies was significantly higher in group $C$（given placebo）than in group $A$ （given AAA Ca），suggesting protection by AAA Ca from the occurrence of changes in the projected area of the vertebral bodies，whereas no such significant protec－ tion by $\mathrm{CaCO}_{3}$ was noted，in view of the absence of a significant difference between groups $B$ and $C$ ，as shown in Fig． 5.
On whole body DXA measurement in the first and second years of the study（shown in Fig．6），no signifi－ cant differences were found among the three groups as to changes from the first to the second year in body weight，total body mass，and whole body lean mass （expressed as a percentage of the total body mass）．As to changes in fat mass，expressed as a perce扁种这it） 6 the whole body mass，the first year／second year value in group A（supplemented with AAACa）was significantly lower than that in group $C$（supplemented with

Coefficient of
Variation of
Projected Area of Vertabral Body 24m/Basal (\%)


Fig. 5. Intra-individual variation of the projected area of $\mathrm{L}_{1}-$ $L_{4}$ vertebral bodies. The coefficient of variation of the projected area was significantly lower in group A, given AAA Ca (but not in group B , given $\mathrm{CaCO}_{3}$ ) compared with group C , given placebo, suggesting a protective action against fracture by AAACa, but not by $\mathrm{CaCO}_{3} . m$, months. Mean $\pm$ SEM


Fig. 6. Whole body mass is shown in the upper panel, body weight in the middle panel, and whole body lean mass in the lower panel, expressed in terms of second year/first year values (\%). Open bars represent group A, supplemented with AAA Ca ; shadowed bars, group B , supplemented with $\mathrm{CaCO}_{3}$; and closed bars, group C, supplemented with placebo. No significant differences were found among the three groups, and all values remained almost constant
2nd year/1st year(\%)

Mean $=\operatorname{SEM}$


Group A Group B Group C

Mineral Mass


Group A Group B Group C

Fig. 7. Whole body mineral mass is shown in the right panel and whole body fat mass is shown in the in the left panel, with the second year value expressed as a percentage of the value in the first year. Open bars represent group A, supplemented with AAA Ca; shadowed bars, group B, supplemented with $\mathrm{CaCO}_{3}$; and closed bars, group C, supplemented with placebo. While the changes in the total mineral mass were not significantly different among the three groups, increase of fat mass was significantly greater in group $C$, supplemented with placebo, than in group A, supplemented with AAA Ca. No significant difference was found between groups $B$ and $C$
placebo), indicating an inhibition of fat accumulation by AAA Ca supplementation. However, no significant difference was found between group B (supplemented with $\mathrm{CaCO}_{3}$ ) and group C (supplemented with placebo). The change in total mineral mass as a percentage of the total body mass suggested a slightly smaller loss in group A than in the other groups, without significant difference (Fig. 7).

As to the regional distribution of bone mineral content, AAA Ca, but not $\mathrm{CaCO}_{3}$, supplementation significantly decreased the bone mineral content of the head, expressed as a percentage of the whole body mineral content, over placebo supplementation, while changes in the mineral content of the arms, trunk, and legs were not significantly different among the three groups (Fig. 8).


Fig. 8. Regional distribution of bone mineral content in head, arms, trunk, and legs; second year values are expressed as percentages of the first year values. Open bars represent group A, supplemented with AAA Ca; shadowed bars, group B, supplemented with $\mathrm{CaCO}_{3}$; and closed bars, group C , supplemented with placebo. The head bone mineral content was significantly decreased in group A compared with group C, but no significant difference was found between groups $B$ and C. No significant difference was found among the three groups as to the changes in the bone mineral content of the arms, trunk, or legs

## Discussion

Active absorbable algal calcium (AAA Ca), produced by heating oyster shell and seaweed in vacuo, is readily absorbed from the intestine [7], and significantly increased lumbar BMD in elderly women over the level in the placebo-supplemented group in a 2 -year prospective, randomized double-blind study (Katsuragi Calcium Study) [1], whereas supplementation with the same amount of calcium, as $\mathrm{CaCO}_{3}$, showed an effect that was not significantly better than the placebo. Peripheral computed tomography of the distal radius made it possible to detect the effect of AAA Ca in increasing trabecular BMD at the distal radius in a double-blind comparison with $\mathrm{CaCO}_{3}$ and placebo in postmenopausal women in a 4 -month period $[8,9]$.

In the present study, DXA data on the lumbar spine from the Katsuragi Calcium Study were reanalyzed to assess the degree of spondylotic deformity, expressed as intra-individual coefficient of variation of $\mathrm{L}_{1}-\mathrm{L}_{4} \mathrm{BMD}$. Lateral X-ray pictures of the thoracic and lumbar spine were examined to detect the occurrence of new fracture, along with calculation of intra-individual variation of the projected area of the $L_{1}-L_{4}$ vertebral bodies. Whole body DXA data obtained in the first and second year of the Katsuragi Calcium Study were also analyzed to define the effect of AAA Ca on total body mineral
content, lean content, and fat content in comparison with the effect of $\mathrm{CaCO}_{3}$ and placebo.

Although lateral spine X -ray films at the beginning and end of the study were available for only a small number of subjects in each group, the significantly lower second year/first year (\%) value for new vertebral fracture in group A (supplemented with AAA Ca) than in group C (given placebo) tends to support the protective action of AAA Ca against fracture through an increase of lumbar BMD , whereas supplementation with $\mathrm{CaCO}_{3}$ showed no significant protective effect over placebo [2]. Compression fracture of the vertebra decreases the projected area of the vertebra most dramatically with a rise in the CV, but spondylotic deformity, even with osteophyte formation, is expected to increase the projected vertebral area only slightly. The significantly lower intra-individual CV of the projected area of the vertebral bodies in group A (given AAA Ca), but not in group B (given $\mathrm{CaCO}_{3}$ ) compared with group C (given placebo) also supports the protective action of AAA Ca but not $\mathrm{CaCO}_{3}$ on vertebral fracture (Fig. 5).
The intra-individual variation of $\mathrm{L}_{1}-\mathrm{L}_{4}-\mathrm{BMD}$, expressed as the CV, was suggested to be one of the manifestations of spondylotic and osteoarthritic deformity [2-6], based on a high correlation with X-ray findings of spondylosis deformans, with both conditions increasing markedly with age, although some minor influence of vertebral compression deformity on the intra-individual variation of lumbar BMD cannot be ruled out. Lumbar spine BMD started to increase from around the sixth month of supplementation in the present study, and intra-individual variation of $\mathrm{L}_{1}-\mathrm{L}_{4}-\mathrm{BMD}$ (CV; SD expressed as a percentage of the mean), also increased, somewhat later than BMD in group C over group A, whereas it did not increase in group B. SD itself, which was strongly dependent on the mean, did not change in group $A$ despite the rise in mean BMD. In the analysis of the $S D$ and $C V$ of the lumbar spine BMD, a high dependency of SD on the mean BMD was found, but the CV (corrected SD expressed as a percentage of the mean) is free of such dependence. Both the CV and Xray findings of spondylotic deformity were found to increase in parallel with age in males and females, but the SD itself increased with age only in males (with a relatively mild change in the mean BMD with age) and not in females, with a marked fall of mean BMD being shown with age. The intra-individual CV but not the SD of lumbar BMD thus appears to reflect the degree of spondylotic change [6].
Spondylosis deformans and osteoarthritis were once thought to be distinctly different and even incompatible with osteoporosis both etiologically antexamptigally. Nevertheless, the coexistence of these two diseases is rather frequent, especially in postmenopausal women with osteoporosis and osteoarthritis of the knee. Both
degenerative joint disease and osteoporosis represent major causes of incapacitating backache and joint pain, which are a distinct threat to the quality of life in the aging population. In DXA of the lumbar spine, a decrease in BMD is naturally a gold standard for the diagnosis of osteoporosis, whereas an artifactual increase in lumbar spine BMD is frequently encountered in subjects with spondylosis deformans or osteoarthritis of the spine, because of secondary changes such as osteophyte formation, eburnation, and localized hyperostosis; this could explain a possible source of misconception on the "incompatibity" of osteoporosis and osteoarthritis. These two groups of diseases, indeed, may be based on a common etiology of calcium deficiency $[10,11]$. Calcium deficiency, due to insufficient intake, decreased intestinal absorption, increased urinary loss, vitamin $D$ deficiency (due to decreased renal calcitriol synthesis), estrogen deficiency, corticosteroid excess, and other causes prompts increased parathyroid hormone (PTH) secretion. PTH stimulates bone resorption and Ca release from bone and Ca entrance into cartilage along with excessive physical load. Increase of the Ca content of cartilage causes its hardening and susceptibility to physical stress, leading to the wearing out and subsequent disappearance of cartilage. The resulting direct bone-to-bone contact evidently causes many of the osteoarthritic and spondylotic changes.
The failure to achieve a significant increase in total body mineral content in 2 years of AAA Ca supplementation may be due to the predominant contribution of cortical bone to the total body mineral content. In the Katsuragi Calcium Study [1], radial cortical BMD also failed to increase during this period. Rather unexpectedly, a significant decrease in total body fat content relative to whole body mass was noted on supplementation with AAA Ca over against placebo-supplemented controls, but supplementation with $\mathrm{CaCO}_{3}$ caused no significant decrease in fat content from the level in the placebo group. Whole body mass, lean mass, and body weight remained relatively constant through the study period in each group. An increase of fat mass was reported to be associated with increased BMD through an increase of weight load, in part [12-14]. Because exercise tends to increase bone mass and decrease fat mass [15], it is conceivable that AAA Ca, by increasing the range of activity, acts like exercise to decrease fat mass. In obesity, on the other hand, Ca deficiency, secondary hyperparathyroidism, and increased intracellular free Ca in adipocytes may be present [16]. Readily absorbable AAA Ca is probably effective to minimize such fat accumulation due to secondary hyperparathyroidism, another example of the calcium paradox.

A significant decrease in the mineral distribution in the head portion, the only nonweight-bearing portion of the body, along with increases in other weight-bearing
or active parts, on supplementation with AAA Ca, but not $\mathrm{CaCO}_{3}$, over that with placebo may also reflect an increase in the level of physical activity or some metabolic effect similar to such an increase in response to AAA Ca but not to $\mathrm{CaCO}_{3}$. Age-related increases in head mineral content, with a tendency toward decreases in other body parts, especially in the legs, was reported and explained by decreasing muscle strength and physical activity during aging [6]. The decrease in head mineral content on supplementation with AAA Ca may therefore represent a process of skeletal rejuvenation by prompting physical activity or a metabolic enhancement that is similar to physical activity. The striking parallelism of these metabolic effects of AAA Ca (but not $\mathrm{CaCO}_{3}$ ) over placebo suggests that AAA Ca may be more useful than $\mathrm{CaCO}_{3}$ as a nutritional supplement.

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Exhibit 7

# An interview with Takuo Fujita, M.D. President, Osteoporosis Foundation of Japan Founder, Calcium Research Institute of Japan 

Dr Fujita, please tell us about your background
I am a physician, clinical investigator and radio technologist. I received my degree of Doctor of Medicine from the University of Tokyo in 1952. As a recipient of the Fulbright fellowship I continued my studies at the University of Buffalo from 1952 up to 1956. As one of the pioneers of calcium studies I studied calcium metabolism and bone disease at the University of Tokyo and at Kobé University.

Tell us of your current activities in calcium research
I am the president of the Japan Osteoporosis Foundation and director of the Calcium Research Institute so 1 am very active in every aspect of calcium studies, including patient studies and clinical investigations.

How many studies have you published on calcium?
Four hundred and twenty, all in peer review joumals.
How long have you been researching calcium and osteoporosis?
About 46 years. I began in 1953 at the University of Buffalo Chronic Disease Research Institute. At that time I came in contact with a serious disease of calcium metabolism-kidney stones in patients with poliomyelitis (polio). I was actually led by a personal motive. At that time there was a great polio epidemics in this country and many young people - remember many of themsuffered from acute poliomyelitis. What happened is, they suddenly lost use of their muscles. They became paralyzed and couldn't move their bones any more. All the calcium came out of the bone causing through the kidney in the urine. They formed huge kidney stones. The kidney lost its function and patients died of the kidney stones. This was very serious and moved me profoundly. I thought there must be something we could do to control calcium metabolism.

What is osteoporosis? How serious a disease is it?
Osteoporosis is weak, breakable, brittle bone, which occurs as a consequence of calcium loss from bone. Bone without calcium is very weak and if we don't take enough calcium, or if we lose too much, our bodies become calcium deficient. Since $99 \%$ of calcium in the body is in the bone, bone is the first part of the body to be affected.

Why is osteoporosis often considered a woman's disease?
Men also lose calcium, but women undergo a very dramatic event at the time of menopause. A sudden-decrease-in-estrogen (fematehormone) brings-menstruation-to an-end-and triggers-a very rapid loss of bone-calcium. This is called post-menopausal osteoporosis. We all paid too much attention to this one event and we thought that post-menopausal osteoporosis was everything. That's why for so long we considered osteoporosis a women's disease. Certainly, it occurs-more-frequently-in-women,-and-earlier-too. After the-age-of fifty, women-are exposed-to increased risk of osteoporosis, whereas men reach an equivalent risk factor much later-maybe around age seventy. So the risks are delayed.

So as men live longer and longer, would you expect to see their osteoporosis risk approaching that of women?
Yes. One of the reasons that so many men don't suffer from osteoporosis is that they die before women. I believe average life expectancy for American men is about seventy-three or seventy-four-it's seventy-seven in Japan-but even among women the most severe forms of osteoporosis occur after age seventy-around seventy-five. So, men don't have the same
opportunity to suffer from osteoporosis. That is one reason. The other is the slow start of osteoporosis in males.

## Why is osteoporosis called the Silent Killer?

Osteoporosis doesn't provoke any noticeable symptoms in the beginning-not for some years. Only when the bone actually breaks or deforms and the osteoporosis is advanced does it become apparent. To diagnose osteoporosis at an earlier stage requires measurement of bone mass, and bone mass measurement has not been available until very recently. So we don't know when osteoporosis is becoming a problem. So that's why we call it a 'silent; disease. We call it a 'killer' because it is by no means harmless. It is as terrible a killer as myocardial infarctions or strokes. The only difference is that osteoporosis for a woman or for a man progresses more slowly than a myocardial infarction. It takes years to provoke a hip fracture, for example. The hip is the largest bone in the body. Bone density diminishes over many years and patients gradually experience difficulty rising and walking. Confinement to bed is very common. Then they develop thrombosis, pneumonia-all these diseases which cause them to slowly die. That's why we call it the Silent Killer, or the Silent Epidemic.

## What is the role and importance of calcium in the human body?

Calcium is the fifth largest component of the human body after carbon, hydrogen, nitrogen and oxygen, the constituents of organic compounds. It is the most abundant mineral in the body. That makes it very important. Ninety-nine percent of calcium is in the bone, but the remaining one percent is distributed throughout the cells. In each cell and of course in blood there's always some calcium, and this calcium outside the bone is even more important than the calcium that's giving strength to the bone. All cells-hormone secreting cells, heart cells, liver cells, kidney cells and brain cells-need calcium to perform their functions. That's why calcium is vital to human beings.

You've been conducting research on a special form of calcium. Can you tell us about it? Not all calcium preparations are alike. Some are more easily absorbed than others. Generally speaking, calcium is one of the least absorbable compounds. For example: sugar. If you eat something sweet, almost $100 \%$ is absorbed immediately, including vitamins and other materials. But only $20 \%$ or so of the calcium you eat is absorbed. This is a very, very low figure-only onefifth of what we eat! So we have to improve the absorption of calcium in order to really help the body to utilize calcium. We have had a recent breakthrough in the form of AAACa (U.S. brand name is AdvaCAL), which is quite absorbable, unlike all other calcium preparations. We make this by heating oyster shell in a vacuum, then adding some similarly treated algae to this. We call it HA1-Heated Algal Ingredient and this combination of oyster-shell calcium and Algal Ingredient makes it very absorbable-much better than any other calcium preparation so far.

## What are the greatest advantages of AAACa (AdvaCAL) over supplements like calcium

 citrate or calcium carbonate?Well, some preparations are better than others. Calcium citrate is one of the better ones. Calcium carbonate is most commonly used but the body's absorption of calcium carbonate is very poor, unless we have very strong stomach acid. That is why we recommend the use of calcium carbonate when you eat. Calcium contained in your food or taken with food is usually better absorbed than most calcium supplements alone. That's because the gastric acid is released in response to the food. But AAACa is so readily soluble in water that it doesn't even need gastric acid. Anybody can take it. Unless it is readily soluble in water, of course, it doesn't get into the blood. So one advantage of AAACa is high solubility. The second advantage is its high availability prompted by the algal ingredient.

Tell us about your research on osteoporosis and bone mineral density as affected by AAACa versus other calcium supplements.
To show whether AAACa is really effective against osteoporosis we have to perform bone measurement. Now any studies which are not randomized or placebo-controlled are not considered valid these days, so I did all these procedures with a group of very elderly ladies-in their eighties. These ladies were deficient in calcium and calcium absorption. If we could demonstrate an effect in these ladies it would no doubt help others to have better absorption. So the challenge-the most difficult part first-was to choose a placebo that contains no calcium but which looks exactly like the calcium preparation so that these people didn't actually know which was calcium and which wasn't. Even the doctors were blind to the nature of the drug. That's what we call a double-blind procedure. Neither the doctor nor the patient knows which is which. And we used calcium carbonate too, for a total of three groups-AAACa, calcium carbonate and placebo-for two years. It took quite a long time and some of these patients dropped out for various reasons. But a good number continued for the full twenty-four months and we found a very impressive increase in bone-mineral density (BMD) in those who received AAACa and a very significant fall of BMD in those who took placebo. Everybody is getting older and losing bone, so we expect such a loss. So even if we are able to merely sustain the BMD, that would be very interesting, but there was a significant increase in BMD for AAACa users. This was quite surprising. In fact, no other existing preparation has been able to produce a definite increase in BMD. Calcium carbonate, by the way, just about sustains BMD and is maybe slightly better than placebo, but can't compare with AAACa.

That clinical study was done with elderly patients-a very tough population. Have you studied pre-menopausal women?
Yes. We have studied middle aged women-around fifty to sixty. There are several ways to measure BMD. Some of them are more sensitive than others, so for this study on the middleaged we have chosen the best and most sensitive measurement available-Peripheral Computer Tomography. This method is characterized by separate measurements for cortical (hard) and trabecular (spongy) bone. This spongy bone is more sensitive to the increase of calcium or other drugs because they have a more abundant blood supply, and are more elastic and changeable. By measuring spongy bone of the forearms we demonstrated a $3 \%$ increase of BMD. This was after only four months. It's really amazing because no other method or preparation, calcium or otherwise, has ever demonstrated a significant increase in bone mineral density in just four months.

You mean even drugs like calcitonin and hormones were unable to perform like that? I don't believe so, no. So I was quite excited when I saw these results. The study is all written up but remains to be published.

How did you dose these patients in your-study?
In all these studies we selected 900 mg of elemental calcium a day for both AAACa and calcium carbonate.

You have developed a theory which you call the 'Calcium Paradox.' What exactly does it say?
It's a paradox because we see the opposite of what we would expect. All of us are calcium deficient. I think everybody agrees with that. Everybody also agrees that when we are deficient in blood calcium, the bone will lose its calcium. Whole body calcium deficiency runs parallel to bone calcium deficiency. Calcium deficiency is a cause of osteoporosis, though others may cite other causes-for example estrogen deficiency also contributes to calcium deficiency. We summarize by saying the cause of osteoporosis is calcium deficiency. But the paradoxical part occurs when the parathyroid hormone secretion increases in response to the blood calcium deficiency. The first important thing about calcium is that we should have an abundant supply to keep our bones strong. The next mnst imoortant is its function in heart and brain action, and
muscles. All these vital body functions are maintained by a constant abundance of calcium in the body. If we don't keep calcium levels in the blood constant, the heart stops. Dr Ringer of England demonstrated this many years ago and we still use Ringer's calcium solutions. If you add calcium chloride to a saline (sodium chloride) solution, the heart will beat. Dr Ringer demonstrated this with a frog's heart. He removed the heart, put it in saline solution and the heart stopped. When he added calcium to the solution, the heart began to move. The fact that we need a constant amount of calcium is the beginning of the calcium paradox theory. We must keep our blood calcium constant but we don't eat enough calcium. If this calcium deficiency were to bring down blood calcium, your heart would stop. That's a terrible thing. Fortunately, it doesn't stop because in response to even a very slight fall of blood calcium, the parathyroid hormone takes calcium out of the bone. Compared with the modest needs of the rest of the body, bone is an almost endless supply of calcium. It's like a bank with a large amount of money. If you have a problem, you go to the bank and borrow. The parathyroid hormone is like a cash card. But if you use your cash card enough times, your bank account will become exhausted. That's osteoporosis. And now the paradox begins. Calcium coming out of the bone enters other tissues where there shouldn't be any calcium to begin with. For example, in the blood vessels. Blood vessels should be soft and elastic. Bones should be hard and strong. There shouldn't be too much calcium in the blood vessels. They become hardened. We call this arteriosclerosis, and blood pressure rises. This is the first calcium paradox disease which came to our attention. Deficiency of calcium results in flooding of calcium in the blood vessels. The second calcium paradox disease is perhaps Alzheimer's disease. If calcium levels rise in the brain cells, brain function starts to decline, you start forgetting things and finally you don't know who you are or anything. This is caused by an increase of calcium in the brain cells. Again, this results paradoxically from calcium deficiency. The parathyroid hormone takes calcium out of the bone and puts it in the brain cells. We don't want them to do this but this is one of the unfortunate byproducts of calcium deficiency. There are many other calcium paradox diseases, for example osteoarthritis is a degeneration of cartilage and loss of calcium to bring bone-onbone in scraping contact in the joints. The formation of osteophytes-bone outgrowths-slowly leads to pain, but the increase of calcium in the cartilage is the first event. Loss of calcium from bone leads to increase of calcium in cartilage. There are many other examples, like diabetes mellitus, some cancers-colon cancer is already established to be caused by calcium deficiency. Calcium enters the cell, the cell starts to proliferate, divide and subdivide until it becomes cancerous. So calcium deficiency is the root of all evil and the cause of many diseases associated with aging. This is the calcium paradox.

So you're saying that the parathyroid gland removes calcium from the bones at such a rate that our health is compromised?
Our body should be very wise. It shouldn't make any mistakes. But in this instance I don't know. Sometimes, it does strange things. Why does the parathyroid hormone take an excessive amount of calcium? Because there is so mueh-caleitmin the bones-ten thousand times more than we eat or have in our blood or soft tissue, so even our wise body doesn't exactly do the best thing. That is one thing I don't understand. But we have all the facts and the calcium paradox is only one attempt to explain all these facts. I don't really have an answer.

All your studies so far have been done in Japan, but some people may be concerned that the Japanese diet is different from the North American diet. Would you expect to see similar results in a North American study group?
Well, the Japanese live very long. They have the highest longevity in the world. They say that fish and seaweed is good for them. The sushi bar is quite popular in this country. But the only trouble with the Japanese diet is that it is very low in calcium content. You are taking more calcium here in this country and in the Western world than in Japan. Other countries in Asia like Korea and China also have very low calcium intake, so that may be one reason why calcium is so effective in Japan. But I think we can expect similar effects-maybe not the same but similar-in the United States, because many investigators in the United States also point out
that even Americans are not taking enough calcium. In addition to the intake of calcium we have also to think of the loss of calcium. If you take large amounts of protein or phosphates-if you eat meat and all kinds of delicious foods you're already taking a lot of phosphates and proteinand that will accelerate the loss of calcium in the urine. So we have to consider both sideswhat you are taking and what you are losing. I'm afraid that although Americans are taking more calcium, they're also losing more calcium. So I think we are almost equal. We are taking less calcium, but our calcium loss may also be lower, so l'd expect similar effects.

It's important to note that you were giving your patients about 600 mg of calcium a day with food. According to U.S. figures l've read, that's about what the typical American receives.
That's right. Actually calcium intake varies widely among different countries. Some people take enough calcium-mainly health-conscious people-but elderly people in most countries are not taking enough. Their appetite diminishes and they don't feel right. And of course the problem of sunshine exposure is very important. Without sufficient exposure to sunlight, you can't make enough Vitamin D to stimulate calcium absorption. Some people in the United States are also calcium deficient, like many Japanese, and I don't think there's too much difference in calcium intake.

> In the United States, a calcium and magnesium complex is quite popular. How would you compare that compound with AAACa (AdvaCAL)?
> Well, calcium and magnesium are both important but we don't have to combine them. The ratio of calcium to magnesium is not important, as long as we are taking enough of both. Too much calcium intake is never dangerous, but too much magnesium can be. So I think calcium is the only one of which you can take as much as you want and get away with it, but you shouldn't take too much magnesium. I don't think we have to combine these two. You may take magnesium if it's necessary. Too much calcium may constipate you-it's one of the unavoidable effects of calcium because calcium takes water away from food and makes the stool harder. Magnesium doesn't do that, so that's why magnesium is used against constipation. I already use magnesium along with calcium, but not as a fixed preparation.

AAACa is comprised of calcium hydroxide and calcium oxide, which you have mentioned are highly soluble in water: Can their high solubility produce any side effects or other problems?
Strangely, lencountered no side effects except maybe some constipation in some people. You may feel a little full in your stomach if you take a large amount of calcium but it doesn't mean that calcium decreases the appetite. Hyper-acidic people-who secrete more acid in the stomach-may tend to have ulcers, and calcium neutralizes gastric acid. But when calcium disappears from the stomach there may be a rebound of gastric acid secretion. It doesn't happen in healthy people, only hyper-acidic people have this problem.

You've done some interesting research on calcium and fat reduction. Please describe it. In this group of elderly ladies-the first group we studied-I didn't really expect the effects we saw. We were measuring the whole body-bone, fat and muscle-and in addition to the increase in BMD I found a definite decrease in the fat content of the body. I was at first skeptical because I didn't expect this effect. But it's there. In the placebo-controlled subjects there was a slight increase of fat but among the others there was a definite decrease from $23 \%$ to $18 \%$ fat. Body weight didn't change that much, so it means that AAACa was able to get rid of some of the fat.

Please comment on the incidence of fractures among AAACa users.
Of course, any increase in BMD promises fewer fractures and for women in their eighties, there was no increase in fractures while they were on AAACa, but out of the thirty-placebo-controlled subjects there were three fractures. This number is not large enough but it suggests that

AdvaCAL prevents decrease of bone strength. So it's quite possible that AdvaCAL would prevent fractures.

If the parathyroid gland is clever enough to extract calcium from bone when it's necessary, why doesn't it regulate the amount it selects?
That's a very good question, but. I don't really have an answer.

## Are other factors involved, or is this purely the responsibility of the parathyroid?

 The parathyroid is a very strange hormone. To begin with, there is no parathyroid in fish, but they live easily without it. They are continually inhaling calcium-rich water and have a non-stop supply of calcium. It only develops in creatures living on land, like ourselves. There might be some difference between constant increase in parathyroid hormone and occasional (periodic) increase. Now, is parathyroid hormone good or bad? It must be good because we need parathyroid hormone. But constantly high parathyroid hormone levels are not good. We have statistics showing that people with lower parathyroid hormone live longer and those with higher parathyroid hormone levels die earlier. They don't live long at all.
## Do they die of any particular illness?

Oh, cancer, even osteoporosis. The best thing is, we should have an optimum amount of parathyroid hormone and in general we need lower levels. But sometimes we need elevated parathyroid hormone levels.

Would you describe the parathyroid function as an emergency mechanism?
Yes. It helps us out in an emergency but it would be better if it weren't necessary. We have a group of patients with renal insufficiency-those undergoing dialysis. There we know the parathyroid hormone is very important because if we lose our kidney function, then we can't: make active vitamin $E$. These patients with kidney failure always show a greater calcium deficiency than healthy people and parathyroid hormone levels are always higher. The parathyroid hormone has been identified as one of the toxins leading to uremia-loss of kidney function. So this mistake may occur when the hormone is acting as a toxin, or perhaps there's an excessive amount of hormone in the blood. Optimum parathyroid hormone levels are harmless and don't bring calcium into the soft tissue of the blood vessels, heart or the brain. So the problem may be one of excessive parathyroid hormone secretion. There's no clear answer, I must confess.

## Why is no vitamin D added to AAACa (AdvaCAL)?

Because HAl acts like vitamin D. AAACa was very effective in the group of elderly ladies we studied. They were deficient in vitamin D because they were hospitalized, and even though the sunshine passes through the windows, there are no ultra-violet rays. So most people in hospital become-vitamin $D$ deficient. Also, older patients are always deficient in vitamin $D$. In spite of this AAACa was very effective. We don't need vitamin D because HAl performs the same function. And it's a natural product.

Is it possible that vitamin $D$ is more helpful when taken with some calcium preparations than with others?
Yes. It all depends on the solubility of the product in question. It must be soluble and iodized. Otherwise it just goes through the gut. According to some figure, it is more soluble than others, even calcitonin-five to ten times more soluble. Solubility is very easy to measure by electrical conductivity. Soluble ions conduct electrical current. AAACa is amazingly soluble.

## What is the effect of exercise on osteoporosis?

Exercise will activate the bone cells to prevent calcium loss from bone. And if you stop exercise, the reverse process occurs. You lose bone. So by exercising, you are preventing bone loss. Both exercise and calcium intake are important-we can't substitute exercise for calcium. But if interview with dr. takuo fujita, m.d.
we exercise more, we also stimulate calcium absorption. It increases appetite, so you eat more, and an elevated metabolism stimulates calcium absorption: So all these things aid calcium absorption.

## Is weight-bearing exercise more useful?

Yes. It is physical pressure on bone that stimulates bone cells. But all exercise, weight-bearing or not, stimulates calcium absorption. Swimming, for example, is non weight-bearing. Walking is weight-bearing. Calcium absorption is also affected by emotional factors. Exercise is good relaxation that makes you feel happier and stronger. This is important because you have to be happy. You have to be out of distress to absorb enough calcium. Stress and unhappiness decrease calcium absorption. Adrenaline and cortico-steroid hormones are secreted during stress. They facilitate calcium loss and prevent gut absorption. You can eat a lot of calcium, but if it's taken in a state of harmony, while chatting with friends, for example, then more calcium is absorbed. So what we need are three things: calcium, exercise and happiness. And of course calcium makes you happy. So calcium is everything!

## What about dietary sources of calcium?

Milk is a very common source of calcium, but it also contains a lot of phosphorus, which combines with calcium and prevents it from being absorbed. Tofu is good, but not many North Americans eat it. You can eat small fish with bones, like sardines-even canned sardines. But bone calcium is also rich in phosphorus. The ideal dietary source should be low in phosphorus and high in calcium. For Americans milk is alright. It is readily absorbed. They say that broccoli and kale are better than milk, but they don't contain much calcium and you have to eat such large quantities that it's not practical. In general, milk is alright. If you are high in cholesterol then low-fat milk is all right. But I would recommend AAACa over any dietary source, because it has no phosphorus. It's superior to any calcium found in foods.

What about people who are not suffering from serious osteoporosis but just want to prevent it. We don't want to tell everybody to go on calcium therapy...or do we?
Oh sure-everybody should take calcium. I'm not osteoporotic, but I take it regularly. As a result my EKG went down. Another thing-calcium makes you happy. It works against stress. In Japan we have a very popular TV program called Pocket Monster. It's for kids. Six hundred kids went into convulsions, attacks, seizure because of this show. They got so excited they stopped breathing, then they started to hyperventilate. Calcium has a tranquilizing effect. So kids watching television should take calcium first. It keeps you happy and peaceful. That's why everybody needs calcium and you don't have to be osteoporotic to take it.

So perhaps we could use calcium to promote world peace.
Well, it's strange. You may find me overenthusiastic about calcium, but as the years go by 1
have no reason to reverse myself, becausel-don't find anything-against it. All the-facts go along with my theory.

The only thing against it is constipation?
Not against it, but we expect it. America has a stressfül society like Japan and we you calcium to make you less stressful, so there will be less crime and less juvenile delinquency and all these things. You need calcium in the schools.

## What is the physiological basis for happiness?

Any minor decrease in blood ionized calcium will make you unhappy. The brain or muscles become excited when there's even a slight fall in blood calcium levels, especially ionized calcium. There are two types of calcium-protein-bound and ionized. Although we're talking about ionized calcium, we just say calcium. If there is a slight decrease in calcium then you are more excited and irritable. A readily absorbable calcium will correct the slight decrease of blood calcium promptly. A slight decrease of blood calcium makes everybody uneasy and irritable. I
interview with dr. takuo fujita, m.d.
see a good example in Alzheimer's patients, who become irritable towards the evening. We call it the Sundowning Syndrome. As the sun goes down, they become excited and they suffer from various complexes. For example, a persecution complex makes them see anyone who approaches them as having bad intentions. Even Alzheimer's patients staying at home may be afraid to go out because the world seems a dangerous place. That's why we keep Alzheimer's patients in a closed room and sometimes have to lock the room-otherwise if they go out, especially in the evening, it could be dangerous. They could be hit by a car. But we can prevent sundown syndrome in Alzheimer's patients by giving them calcium in the afternoon. They become quieter. There's a very slight decrease of blood calcium towards evening. Perhaps healthy people experience a slight decrease too, but it's not noticeable, but in Alzheimer's patients it is noticeable. I have already published this study on convulsions in children watching TV. We tried some experiments. We didn't want to produce convulsions in children, so we took teenagers, 18 to 20 year-old students. We gave them some money and they watched TV. They were happy to cooperate. They didn't suffer convulsions but their blood calcium levels declined while watching the show-an action story with an exciting soundtrack. One day we measured their blood calcium. It came up low. The next day, we gave them AAACa two hours before watching the same show. Then, their blood calcium remained constant. They don't feel anything because the drop was minor, but we clearly demonstrated the effect of supplementing calcium. We had to use ionized calcium so that it could be directly measured. This requires special apparatus. I wrote a paper on the subject.

## As opposed to protein-bound?

Yes, because calcium is associated with protein very easily, according to stress or other conditions. The ionized fraction act directly on the brain, and protein acts as a kind of buffer. Usually, we measure total calcium, which doesn't change very easily, but if we measure ionized calcium we can show these effects. Calcium is a kind of hormone, in the same way as vitamin D. Simple minerals like potassium, sodium and all other salts don't have receptors. Receptors are very important. Receptionists in offices who screen everybody coming in are like hormonal receptors. Calcium has a receptor, too. No other mineral have receptors. We call it a calcium sensor, or calcium receptor. It is a treatment for VIPs. Not like ordinary minerals. Some people may think calcium's dangerous because we call it a hormone, but that's not the case. We think of it as like a hormone-as important as a hormone, as specific as hormones to accomplish certain functions. So calcium is very special.

Does it fit the definition of a hormone or are you using this as an analogy?
All hormones have receptors. Calcium is the only mineral with receptors. So we can say that calcium is a unique mineral that is like a hormone. Let's call it the happy hormone!

> Fhese statements have not been evaluated by the Food \& Drug Administration. This product is not intended to treat, cure or prevent any disease. Exercise and a healthy diet with adequate daily calcium intakes may help younger white and Asian women reduce their Osteoporosis risk in later life. Calcium intakes above $2,000 \mathrm{mg}$ are not likely to provide extra benefit.

## Exhibit 8

## INTRODUCTION

Lane Laboratories (the Sponsor) markets a calcium supplement preparation, developed and supplied by Fujix, Inc., of Japan. The source is of uncertain composition, but is based on heat-treated oyster shells, to which a small quantity of an algal extract is added. Lane Laboratories had provisional bioavailability data supplied by Fujix, but was desirous of determining if the supplier's results could be duplicated by a disinterested third party. Accordingly, Lane Laboratories approached the Osteoporosis Research Center of Creighton University to conduct suitable bioavailability tests, comparing the Lane product ("AdvaCal") with another popular calcium supplement ("Citracal" - Mission Pharmaceutical, San Antonio, Tx).

## METHODS

Subjects. Subjects were $\ddot{2} 4$ healthy postmenopausal women, average age $58.5( \pm 5.2)$ yrs. 13 were receiving ERT/HRT and continued throughout the study, and 11 took no HRT. Subjects who habitually had used calcium supplements were asked to abstain beginning 5-7 days prior to beginning the comparative study of AdvaCal and Citracal. In order to ensure similarity of vitamin D status, all subjects were given $25(\mathrm{OH}) \mathrm{D}$ [Calderol®], 20 $\mu \mathrm{g}$ every other day, starting 5-7 days prior to the first test day and continuing for the duration of the study. Pertinent personal information is listed in Table 1 at the end of this report.

All subjects gave signed consent and the project was approved by the Creighton University Institutional Review Board. A copy of the consent form is included in the Appendix, along with copies of other pertinent forms used in the project.

## Investigational Design. The design of the study was a randomized cross-over,

 comparing absorbability within subject. The hypothesis underlying the project was that AdvaCal would be absorbed more efficiently than calcium citrate (in the form of Citracal), and the corresponding null hypothesis was that there was no difference in absorbability between the two products. Each subject was assigned a sequence of "ca" or "ac", where "c" stands for Citracal and "a" for AdvaCal. The sequences were assigned to the subjects in the order of entry, using the random number function of Excel (Microsoft Corporation, Redmond, WA).
## Protocol. After screening and obtaining consent, subjects reported to the ORC in the morning, fasting. A blood sample was taken to establish the baseline serum calcium

 value. Then the subjects were fed a standard light breakfast consisting of two pieces of Center-baked, Italian style, low calcium white bread, toasted, with one pat of butter for each, plus a cup of coffee or tea (without cream or whitener) but with artificial sweetener if desired. Midway during breakfast the subjects swallowed the test products and the time was noted. Then blood samples were drawn at $1,3,5,7$, and 9 hours thereafter for measurement of total serum calcium. Lunch was provided in the hospital, but subjects were instructed to avoid all calcium-rich foods. After completion of the first test day, the subjects resumed their usual routine (except continuing to abstain from calcium supplements where applicable) and returned approximately one week later for the second test in the sequence, when the above routine was repeated. The average interstudy interval was 7.5 days.Analyses. Serum calcium was analyzed by atomic absorption spectrophotometry (AAnalyst 100, Perkin-Elmer, Norwalk, CT). Both calcium products were dissolved in hydrochloric acid and their calcium content analyzed also by atomic absorption.

Test Products. The two test products were Advacal, supplied by Lane Laboratories (Lot No. 6369; Expiration date 7/03), and Citracal (Lot No. OC55; Expiration date 3/02). Six capsules, each labeled to contain 150 mg and analyzed to contain an average of 166.4 mg calcium, constituted the test dose of AdvaCal, and three tablets, labeled to contain 315 mg and analyzed to contain 318.3 mg each, constituted the test dose of Citracal. Thus, the aggregate dose for AdvaCal was 998.4 mg , and for Citracal, 954.9 mg .
The AdvaCal product was further analyzed to determine its homogeneity and calcium density. The standard deviation of the weight of a batch of 15 capsules was $2.17 \%$, and the calcium content of the powder within the capsule was $40.7 \%$ by weight, close to the synthesized, precipitated calcium carbonate.
Statistical Analysis. The primary outcome variable was the area under the curve for the increment in serum calcium above baseline, from 0 to 9 hours (i.e., AUC9), calculated by the trapezoidal method. Statistical significance was tested by repeated measures ANOVA, testing for treatment and order. Pharmacokinetic parameters were estimated using an exponential model and a 0.75 hour time delay between ingestion and absorption, employing PK Analyst (MicroMath, Salt Lake City, UT).

## RESULTS

The principal results of the study are contained in Table 2, which sets forth, for each subject, the serum calcium value at each sampling point for each product, together with the respective $\mathrm{AUC}_{9}$ values and the within-subject difference between products. Fig. 1 presents the aggregated data by product, first for total serum calcium (A) and then for the increment above baseline induced by the absorbed calcium (B).
AUC, for AdvaCal averaged $3.148 \pm 0.307$ (SEM) and for Citracal, $4.386 \pm 0.394$ (SEM). AUC 9 varied within subject, reflecting the usual day-to-day variability in absorptive performance. AUC; was higher for Citracal than for AdvaCal in 17 of the 24 subjects, and higher for AdvaCal in 7. The mean within-subject difference between the paired values for AUC9 (AdvaCal minus Citracal) was $-1.238 \pm 0.385$ (SEM). This difference is statistically significant ( $\mathrm{P}<0.005$ ). The mean arithmetic ratio of AdvaCal to Citracal was $0.804 \pm 0.088$ (SEM).
Pharmacokinetic estimation of $\mathrm{AUC}_{\infty}$, using the data available out to nine hours postingestion, yielded an estimate of 4.10 for AdvaCal and 6.18 for Citracal. Cmax was 0.567 and $0.712 \mathrm{mg} / \mathrm{dl}$ for the increment in serum calcium for the two products, and Tmax was 3.32 and 3.86 hours, respectively.

## DISCUSSION

For products that cannot be labeled with a suitable isotopic tracer, the pharmacokinetic method used in this investigation, i.e., comparing the small rise in serum calcium induced by the absorption of calcium from two or more test products; constitutes the preferred approach to evaluating bioavailability. Absolute absorbability is not available with this method; instead reference is made to another, established product - in this case Citracal. The roughly $20 \%$ lower absorbability of the two sources (as judged from the mean AUC9 ratio) could theoretically mean that calcium citrate was more efficiently absorbed than calcium carbonate. However, that has shown not to be true in a variety of other studies (1-3). In a randomized cross-over design comparing intrinsically labeled calcium citrate with calcium carbonate (1), our group found, if anything, slightly better absorbability for the carbonate salt. Sheikh et al. (2), using the intestinal wash-out method, also found somewhat greater absorbability for the carbonate than for the citrate.
An additional possibility would be that the pharmaceutical formulation altered the intrinsic absorbability of the calcium salt contained in a particular marketed product. Work in our laboratory has confirmed that formulation can be an important determinant of bioavailability. However, in a project just completed in our laboratory, and submitted for publication (3), we compared, using methods essentially the same as those employed in this project, one of the leading marketed calcium carbonate products, with one of the leading marketed calcium citrate products, and found identical absorption curves for the two.

Thus, we conclude that there was something about the AdvaCal product which rendered its calcium slightly less absorbable than that of calcium citrate (and by extension, of other calcium carbonate products, as well, which have, as noted, been shown to be identical to calcium citrate). At the same time it must be said that, while absorbability for AdvaCal is not as good as had been hoped, certainly not superior to that of at least one currently marketed product, it still can be a useful calcium source. If the ratio of the absorbability of the two products is calculated as the simple arithmetic mean of the within-subject ratios, the resulting value ( 0.804 ) narrowly falls within the range for bioequivalence defined by the FDA (i.e., 0.80 to 1.25 ). However, if the ratio is calculated as the geometric mean, as the FDA may require (4), then the ratio falls below 0.80 .

## REFERENCES

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3. Heaney RP, Dowell, MS, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. J Am Coll Nutr (submitted) 2000.
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Table 2. Serum calcium following ingestion of calcium sources


ACal03

| ACaIO3 |  |  |  |  |  |  |  |  |  |  |  |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
| Visit 1 | SCa | $\boldsymbol{a}$ | 9.67 | 9.40 | 9.81 | 10.19 | 9.85 | 9.80 | 88.435 | -0.445 | 0.759 |
|  | Incr $S C a$ |  | 0.00 | -0.27 | 0.14 | 0.52 | 0.18 | 0.13 | 1.405 |  |  |
| Visit 2 | SCa | $\boldsymbol{c}$ | 9.64 | 9.34 | 9.72 | 10.27 | 9.97 | 9.86 | 88.610 |  |  |
|  | Incr $S$ Ca |  | 0.00 | -0.30 | 0.08 | 0.63 | 0.33 | 0.22 | 1.850 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |

ACal04

| Visit 1 | S Ca | $\boldsymbol{c}$ | 9.20 | 9.74 | 10.28 | 10.31 | 9.99 | 9.67 | 90.040 | -4.245 | 0.414 |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
|  | Incr $S$ Ca |  | 0.00 | 0.54 | 1.08 | 1.11 | 0.79 | 0.47 | 7.240 |  |  |
| Visit 2 | SCa | $\boldsymbol{a}$ | 9.31 | 9.56 | 10.19 | 9.49 | 9.53 | 9.37 | 86.785 |  |  |
|  | Incr $S C a$ |  | 0.00 | 0.25 | 0.88 | 0.18 | 0.22 | 0.06 | 2.995 |  |  |

ACal05

| Visit 1 | S Ca | $\boldsymbol{a}$ | 9.71 | 9.74 | 10.28 | 1.0 .24 | 10.13 | 9.83 | 90.595 |  |  |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
|  | Incr $S C a$ |  | 0.00 | 0.03 | 0.57 | 0.53 | 0.42 | 0.12 | 3.205 |  |  |
| Visit 2 | SCa | $\boldsymbol{c}$ | 9.36 | 9.39 | 9.89 | 9.77 | 9.72 | 9.63 | 87.155 |  |  |
|  | Incr $S$ Ca |  | 0.00 | 0.03 | 0.53 | 0.41 | 0.36 | 0.27 | 2.915 |  |  |

ACal06

| Visit 1 | S Ca | $\boldsymbol{a}$ | 9.76 | 9.56 | 10.09 | 10.08 | 9.78 | 9.70 | 88.820 |  | -3.165 | 0.236 |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
|  |  |  | 0.00 | -0.20 | 0.33 | 0.32 | 0.02 | -0.06 | 0.980 |  |  |  |
| Visit 2 | S Ca | $\boldsymbol{c}$ | 9.61 | 9.56 | 10.33 | 10.41 | 10.08 | 9.85 | 90.635 |  |  |  |
|  | Incr $\boldsymbol{S C a}$ |  | 0.00 | -0.05 | 0.72 | 0.80 | 0.47 | 0.24 | 4.145 |  |  |  |

ACal07

| Visit 1 | SCa | $\boldsymbol{a}$ | 9.55 | 9.33 | 9.78 | 10.09 | 9.87 | 9.71 | 87.960 | -0.810 | 0.713 |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
|  | Incr $\boldsymbol{S C a}$ |  |  | 0.00 | -0.22 | 0.23 | 0.54 | 0.32 | 0.16 | 2.010 |  |
| Visit 2 | SCa | $\boldsymbol{c}$ | 9.61 | 9.71 | 9.9 | 10.13 | 9.95 | 9.98 | 89.310 |  |  |
|  | Incr $S C a$ |  | 0.00 | 0.10 | 0.29 | 0.52 | 0.34 | 0.37 | 2.820 |  |  |

Table 2. Serum calcium following ingestion of calcium sources


ACal10

| ACal10 |  |  |  |  |  |  |  | -2.840 | 0.014 |  |  |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
| Visit 1 | SCa | $\boldsymbol{c}$ | 9.84 | 9.82 | 10.48 | 10.41 | 10.01 | 9.99 | 91.440 |  |  |
|  | Incr $S$ Ca |  | 0.00 | -0.02 | 0.64 | 0.57 | 0.17 | 0.15 | 2.880 |  |  |
| Visit 2 | SCa | $\boldsymbol{a}$ | 10.07 | 10.17 | 10.41 | 10.12 | 9.83 | 9.66 | 90.670 |  |  |
|  | Incr $S C a$ |  | 0.00 | 0.10 | 0.34 | 0.05 | -0.24 | -0.41 | 0.040 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |

ACal11

| Visit 1 | S Ca | $\boldsymbol{c}$ | 9.61 | 9.59 | 9.94 | 10.59 | 10.25 | 10.26 | 91.010 |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
|  | Incr S Ca |  | 0.00 | -0.02 | 0.33 | 0.98 | 0.64 | 0.65 | 4.520 |
| Visit 2 | SCa | $\boldsymbol{a}$ | 9.85 | 9.85 | 10.19 | 10.66 | 10.01 | 9.97 | 91.390 |
|  | Incr S Ca |  | 0.00 | 0.00 | 0.34 | 0.81 | 0.16 | 0.12 | 2.740 |

ACal12

| ACal12 |  |  |  |  |  |  |  | -0.250 | 0.937 |  |  |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
| Visit 1 | SCa | $\boldsymbol{a}$ | 9.41 | 9.53 | 10.34 | 10.1 | 9.68 | 9.14 | 88.380 |  |  |
|  | Incr $S$ Ca |  | 0.00 | 0.12 | 0.93 | 0.69 | 0.27 | -0.27 | 3.690 |  |  |
| Visit 2 | SCa | $\boldsymbol{c}$ | 9.15 | 9.25 | 9.62 | 9.96 | 9.65 | 9.38 | 86.290 |  |  |
|  | Incr SCa |  | 0.00 | 0.10 | 0.47 | 0.81 | 0.50 | 0.23 | 3.940 |  |  |

ACal13

| Visit 1 | S Ca | $\boldsymbol{a}$ | 9.82 | 9.86 | 10.24 | 10.36 | 10.33 | 9.98 | 91.540 | -0.705 | 0.818 |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
|  | Incr $S$ Ca |  |  | 0.00 | 0.04 | 0.42 | 0.54 | 0.51 | 0.16 | 3.160 |  |
| Visit 2 | SCa | $\boldsymbol{c}$ | 9.83 | 9.78 | 10.57 | 10.58 | 10.28 | 9.89 | 92.335 |  |  |
|  | Incr $S$ Ca |  | 0.00 | -0.05 | 0.74 | 0.75 | 0.45 | 0.06 | 3.865 |  |  |

ACal14

|  |  |  |  |  |  |  |  | -1.335 | 0.834 |  |  |
| :--- | :--- | :--- | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: | ---: |
| Visit I | SCa | $\boldsymbol{c}$ | 9.20 | 9.52 | 10.59 | 10.51 | 10.06 | 9.63 | 90.830 |  |  |
|  | Incr $S C a$ |  | 0.00 | 0.32 | 1.39 | 1.31 | 0.86 | 0.43 | 8.030 |  |  |
| Visit 2 | SCa | $\boldsymbol{a}$ | 9.12 | 9.47 | 10.47 | 10.21 | 9.65 | 9.35 | 88.775 |  |  |
|  | Incr $S C a$ |  | 0.00 | 0.35 | 1.35 | 1.09 | 0.53 | 0.23 | 6.695 |  |  |

Table 2. Serum calcium following ingestion of calcium sources

| ACal15 |  | Time (hrs) |  |  |  |  |  |  | $A U C 9$ | $a-c$ | $a / c$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Subst | 0 | 1 | 3 | 5 | 7 | 9 |  |  |  |
|  |  |  |  |  |  |  |  |  |  | 0.495 | 1.361 |
| Visit 1 | $S C a$ | $c$ | 9.50 | 9.66 | 9.67 | 9.80 | 9.59 | 9.51 | 86.870 |  |  |
|  | Incr S Ca |  | 0.00 | 0.16 | 0.17 | 0.30 | 0.09 | 0.01 | 1.370 |  |  |
| Visit 2 | $S \mathrm{Ca}$ | $a$ | 9.41 | 9.4 | 10.13 | 9.7 | 9.35 | 9.39 | 86.555 |  |  |
|  | Incr S Ca |  | 0.00 | -0.01 | 0.72 | 0.29 | -0.06 | -0.02 | 1.865 |  |  |
| ACal16 |  |  | - |  |  |  |  |  |  | 3.90 | 0.514 |
| Visit 1 | S Ca | $c$ | 9.40 | 9.52 | 10.23 | 10.81 | 10.63 | 10.301 | 92.620 |  |  |
|  | Incr S Ca |  | 0.00 | 0.12 | 0.83 | 1.41 | 1.23 | 0.90 | 8.020 |  |  |
| Visit 2 | SCa | $a$ | 9.22 | 9.1 | 9.87 | 10.03 | 9.65 | 9.74 | 87.100 |  |  |
|  | Incr S Ca |  | 0.00 | -0.12 | 0.65 | 0.81 | 0.43 | 0.52 | 4.120 |  |  |
| ACal17 |  |  |  |  |  |  |  |  |  | -2.195 | 0.601 |
| Visit 1 | $S C a$. | $a$ | 9.10 | 9.26 | 9.73 | 9.37 | 9.65 | 9.27 | 85.210 |  |  |
|  | Incr S Ca |  | 0.00 | 0.16 | 0.63 | 0.27 | 0.55 | 0.17 | 3.310 |  |  |
| $V$ isit 2 | $s C a$ | $c$ | 9.38 | 9.69 | 10.17 | 10.14 | 10.09 | 9.9 | 89.925 |  |  |
|  | Incr S Ca |  | 0.00 | 0.31 | 0.79 | 0.76 | 0.71 | 0.52 | 5.505 |  |  |
| ACal18 |  |  |  |  |  |  |  |  |  | 1.650 | 1.728 |
| Visit 1 | $\boldsymbol{S C a}$ | $a$ | 9.35 | 9.54 | 9.77 | 10.14 | 9.85 | 9.561 | 88.065 |  |  |
|  | Incr S Ca |  | 0.00 | 0.19 | 0.42 | 0.79 | 0.50 | 0.21 | 3.915 |  |  |
| Visit 2 | SCa | $c$ | 9.47 | 9.58 | 9.85 | 9.8 | 9.72 | 9.65 | 87.495 |  |  |
|  | Incr S Ca |  | 0.00 | 0.11 | 0.38 | 0.33 | 0.25 | 0.18 | 2.265 |  |  |
| ACal19Visit 1 |  |  |  |  |  |  |  | . |  | -4.340 | 0.268 |
|  | $S C a$ | $c$ | 9.78 | 9.8 | 11.03 | 10.75 | 10.33 | 10.14 | 93.950 |  |  |
|  | Incr S Ca |  | 0.00 | 0.02 | 1.25 | 0.97 | 0.55 | 0.36 | 5.930 |  |  |
| Visit 2 | SCa | $a$ | 9.69 | 9.57 | 10.07 | 10.04 | 9.79 | 9.80 | 88.800 |  |  |
|  | Incr S Ca |  | 0.00 | -0.12 | 0.38 | 0.35 | 0.10 | 0.11 | 1.590 |  |  |
| ACal20Visit 1 |  |  |  |  |  |  |  |  |  | 1.010 | 1.277 |
|  | SCa | $c$ | 9.38 | 9.28 | 10.05 | 10.38 | 9.60 | 9.40 | 88.070 |  |  |
|  | Incr S Ca |  | 0.00 | -0.10 | 0.67 | 1.00 | 0.22 | 0.02 | 3.650 |  |  |
| Visit 2 | SCa | $\boldsymbol{a}$ | 9.37 | 9.29 | 10.28 | 10.34 | 9.79 | 9.55 | 88.990 |  |  |
|  | Incr S Ca |  | 0.00 | -0.08 | 0.91 | 0.97 | 0.42 | 0.18 | 4.660. |  |  |
| ACal21Visit 1 |  |  |  |  |  |  | . |  |  | 0.540 | 1.246 |
|  | $S C a$ | $c$ | 9.54 | 9.75 | 10.1 | 9.78 | 9.72 | 9.46 | 88.055 |  |  |
|  | Incr S Ca |  | 0.00 | 0.21 | 0.56 | 0.24 | 0.18 | -0.08 | 2.195 |  |  |
| Visit 2 | SCa | $a$ | 9.66 | 9.75 | 10.13 | 10.19 | 9.91 | 9.76 | 89.675 |  |  |
|  | Incr S Ca |  | 0.00 | 0.09 | 0.47 | 0.53 | 0.25 | 0.10 | 2.735 |  |  |

Table 2. Serum calcium following ingestion of calcium sources

|  |  | Time (hrs) |  |  |  |  |  |  | AUCя | $a-c$ | $a / c$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Subst | 0 | 1 | 3 | 5 | 7 | 9 |  |  |  |
| ACal22 |  |  |  |  |  |  |  |  |  | -2.050 | 0.518 |
| Visit 1 | $S C a$ | $a$ | 9.59 | 9.78 | 9.99 | 9.87 | 9.74 | 9.85 | 88.515 |  |  |
|  | Incr S Ca |  | 0.00 | 0.19 | 0.40 | 0.28 | 0.15 | 0.26 | 2.205 |  |  |
| $V$ isit 2 | $s \mathrm{Ca}$ | $c$ | 9.47 | 9.48 | 10 | 10.29 | 10.04 | 9.87 | 89.485 |  |  |
|  | Incr S Ca |  | 0.00 | 0.01 | 0.53 | 0.82 | 0.57 | 0.40 | 4.255 |  |  |
| ACal23 |  |  |  |  |  |  |  |  |  | -0.830 | 0.803 |
| Visit 1 | SCa | $a$ | 9.73 | 9.84 | 10.45 | 10.18 | 10.00 | 10.07 | 90.955 |  |  |
|  | Incr S Ca |  | 0.00 | 0.11 | 0.72 | 0.45 | 0.27 | 0.34 | 3.385 |  |  |
| Visit 2 | SCa | $c$ | 9.65 | 9.76 | 10.23 | 10.31 | 10.23 | 10.06 | . 91.065 |  |  |
|  | Incr S Ca |  | 0.00 | 0.11 | 0.58 | 0.66 | 0.58 | 0.41 | 4.215 |  |  |
| ACal24 |  |  |  |  |  |  |  |  |  | -2.405 | 0.543 |
| Visit 1 | $S C a$ | $c$ | 9.18 | 9.20 | 10.05 | 9.95 | 9.87 | 9.75 | 87.880 |  |  |
|  | Incr S Ca |  | 0.00 | 0.02 | 0.87 | 0.77 | 0.69 | 0.57 | 5.260 |  |  |
| Visit 2 | SCa | $a$ | 9.28 | 9.25 | 9.93 | 9.47 | 9.75 | 9.56 | 86.375 |  |  |
|  | Incr S Ca |  | 0.00 | -0.03 | 0.65 | 0.19 | 0.47 | 0.28 | 2.855 |  |  |
|  |  |  |  |  |  |  |  | Mean |  | -1.238 | 0.804 |
|  |  |  |  |  |  |  |  | StDev |  | 1.888 | 0.430 |
|  |  |  |  |  |  |  |  | N |  | 24 | 24 |
|  |  |  |  |  |  |  |  | SEM |  | 0.385 | 0.088 |
|  |  |  |  |  |  |  |  | t |  | -3.213 |  |

A
TOTAL SERUM CALCIUM


B
INCREMENT IN SERUM CALCIUM


## Exhibit 9

# Absorbability and Cost Effectiveness in Calcium Supplementation 

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Key words: calcium absorption, calcium carbonate, calcium citrate, bioavailability, cost-effectiveness
Background: Cost-ettectaveness of calcuum supptementation depenas not ony on tee cost or the proauct out on the efficiency of its absorption. Published cost-benefit analyses assume equal bioavailability for all calcium sources. Some published studies bave suggested that there are differences in both the bioavailability and cost of the inajor calcium supplements.

Design: Randomized four period, three-way cross-over comparing single doses of off-the-shelf commercial calcium supplements containing either calcium carbonate or calcium citrate compared with a no-load blank and with encapsulated calcium carbonate devoid of other ingredients; subjects rendered fully vitancin D-replete with $10 \mu \mathrm{~g} / \mathrm{day} 25(\mathrm{OH}) \mathrm{D}$ by mouth, starting one week prior ta the first test.

Subjects: 24 postmenopausal women
Methods: Pharmacolineric analysis of the increment in scrum total and ionized calcium and the decrement in serum IPTH induced by an oral calcium load, based upon multiple blood samples over a 24 -hour period; measurement of the rise in urine calcium excretion. Data analyzed by repeated measures ANOVA. Cost calculations based on average retail prices of marketed products used in this study from April through October, 2000.

Results: All three calcium sources (marketed calcium carbonate, encapsulated calcium carbonate and marketed calcium cirate) produced identical 24 -hour time courses for the increment in total serum calcium. Thus, these were equally absorbed and had equivalent bioavailability. Urine calcium rose slightly more with the citrate than with the carbonate preparations, but the difference was zot significant. Serum iPTH showed the expected depression accompanying the rise in serum calcium, and there were no significant differences between products.

Conclusion: Given the equivalent bionvuilability of the two marketed products, the cost benefit analysis favors the less expensive carbonate prociuct.

## INTRODUCTION.

There is general acceptance of the importance of achieving adequate calcium intakes throughout life, and in most adults effort in that regard means taking some form of calcium supplement. Over half the women enrolled in the Women's Health Initiative reported using supplements, and that figure rose to nearly $60 \%$ in women over age 70 [1]. While calcium supplementation has generally been considered a cost effective intervention [2,4], much depends upon the cost of the preparation. Thus Torgerson and Kanis, in the UK, calculated that calcium

Was not cost effective for a preparation they priced at - $\$ 0.50 / \mathrm{g}$ in current dollars [5]. Lowering that cost modestly produced a more favorable relationship. Bendich, et. al.' [4] found that calcium supplementation at 1209 mgdayy and a cost of $\$ 0.10-$ 0.12 g was cost effective for all US women 75 years of age or older when calculated against the costs of care associated only with hip fracture. If the endpoint was increase in bone mineral density and its associated lower total fracture risk, then calcium supplementation was cost effective even with universal supplementation of all US men and women 65 years of age or older.

An additional consideration, given virtually no attention to

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date, involves factoring in bioavailability of the calcium source. Most, if not all, analyses to date have assumed equivalent bioavailability for different salts and different consumer formulations. Recent publications by Heller et al. $[6,7]$ suggested that this might not be the case. The authors reported absorbability for a calcium citrate supplement superior to that of a commercially marketed calcium carbonate product. Since the two salts, in pure form, had been shown in several studies to be absorbed equally well [8-10], a question arose as to whether differences in pharmaceutical preparation of marketed products might have interfered with or enhanced the absorbability of one or the other preparation. Such absorptive effects, if they exist, would alter cost effectiveness calculations, once calcium actually delivered into the blood stream becomes the basis for the computation.

Accordingly we set out to compare two commercial supplements, using standard pharmacokinetic methods, both with one another and with non-pharmaceutical calcium carbonate intgested without excipients. This communication describes the results of this investigation. Additionally, we then used the bioavailability data to calculate the costs associated with providing the two commercially available calcium salts to the US population at greatest risk of hip fracture.

## MATERIALS AND METHODS

## Subjects

Subjects were 24 postmenopausal women aged $56.1 \pm 7.1$ years and in good general health. Their BMI was $29.3 \pm 5.2$ $\mathrm{kg} / \mathrm{m}^{2}$. Thirteen subjects were receiving estrogen replacement therapy, and the remaining 11 were not. One was AfricanAmerican; the others were Caucasian. Subjects taking calcium supplements were asked to abstain throughout the course of the study, starting at least one week in advance of the first test. Additionally, subjects were counseled by our research dietitian to hold calcium from dietary sources to under $400 \mathrm{mg} / \mathrm{day}$. mainly by avoiding all dairy products. Also, they were in structed to avoid high sodium foods (such as commercial fast foods and canned soups or soup mixes) starting two days prior to and including each test day. To eliminate any variahility is absorptive performance due to vitamin $D$ insufficiency or to seasonal change in vitamin D status, all subjects were given 10 $\mu \mathrm{g} 25(\mathrm{OH}) \mathrm{D}_{3}$ (Calderol 1 , Organon, West Orange, NJ )/day starting one week before the first test and continuing throughout the study. This dose is approximately equivalent to 1000 IU ( $25 \mu \mathrm{~g}$ ) of cholecalciferol, but produces a rapid elevation of serum $25(\mathrm{OH}) \mathrm{D}$, in contrast with the five month time-co-equilibrium required when using cholecalciferol. Further, this dose is the amount required, at Omaha's latitude, to bring serum $25(\mathrm{OH}) \mathrm{D}$ concentration up to $32 \mathrm{ag} / \mathrm{mLL}(80 \mathrm{nmol} / \mathrm{L})$, a level widely considered to be the lower limit of physiological normal. The study was approved by the Creighton Universiry

Instíutional Review Board, and each subject gave written consent.

## Design

The sudy was a four-period, three-way randomized crossover, within-subject design, with each individual receiving Os-Cal(a) (a product manufactured by GlaxoSmithkline and consisting of calcium carbonate derived from oyster shell), Citracal8 (a product manufactured by Mission Pharmacal and consisting of calcium citrate), a gelatin capsule containing precipitated calcium carbonate or an empty gelatin capsule (the blank). The test source was ingested midway through a standard light breakfast containing two pieces of Italian-style white bread (Center-baked from unenriched flour), toasted and buttered, together with a cup of coffee, tea or water (with artificial sweetener if desired), plus additional water to ensure adequate urine volume. Blood samples were taken at $0,1,3,5,7,9,12$, and 24 hours for measurement of total and ionized calcium and parathyroid hormone (PTH). Urine was collected in two pools, from 0 to 5 hours, and from 5 to 24 hours, and was analyzed for calcium, creatinine and sodium. Calcium sources were given only on the test day and only at the breakfast meal. The noon meal was provided by Center staff between the 5 and 7 hour blood draws and was designed to be low in both calcium and sodium. The evening meal was ingested between the 9 and 12 hour blood draws. Tests were separated typically by seven days; in this way the entire suite of studies was completed for most subjects within a 22 -day period so as to minimize temporal variability in absorptive performance.

## Test Sources

For the two commercial products (Os-Cal $(8)$ and Citracal( 8 ), the sources were purchased from a retail pharmacy. The labeled content of elemental calcium for the $\mathrm{Os}-\mathrm{Cal}$ ( was 500 mg , plus 200 I.U. of vitamin D (Control No. 9K2228; exp. date 11/01). In order to approximate the load size of the $\mathrm{Os}-\mathrm{CalB}$, the Citracal(8) dose required a combination of two different formulations, one labeled to contain 200 mg elemental calcium (Lot 9D12; exp. date 4/02) and the other 315 mg plus 200 I.U. vitamin D (Lot 9E86; exp. date 5/01). Precipitated calcium carbonate was prepared in the Center's laboratory by dissolving reagent grade calcium chloride in distilled water, heating to $80^{\circ} \mathrm{C}$ with stirring and adding a slight stoichiometric excess of a heated aqueous solution of sodium carbonate, timed so that the reaction was completed within one minute. The resulting precipitate was collected on a fritted glass filter, washed with deionized water to remove adsorbed sodium chloride, dried at $90^{\circ} \mathrm{C}$ overnight, ground in a mortar and packed loosely into tared gelatin capsules in sufficient quantity to provide a 500 mg calcium load per dose. All preparations were chemically analyzed; actual ingested loads of. calcium were as follows: for $\mathrm{Os}_{5} \mathrm{Cal}(8,503 \mathrm{mg}$; for CitracalB, 516 mg , and for precipitated calcium carbonate, 497 mg .

## Analytical Methods

Calcium in serum, urine and the ingested sources was analyzed by atomic absorption spectrophotometry (AAnalyst 100 , Perkin-Elmer, Norwalk, CT), creatinine in urine by an auto analyzer method (Chiron Express Plus, Ciba Conning Diaguostics, Medfield, MA) and sodium in urine by an ion selective electrode method (Cobas Integra, Roche Diagnostics, Basel, Switzerland). Serum ionized calcium was analyzed under standardized test conditions by an ion selective electrode method (Nova Nucleus, Nova Biomedical, Waltham, MA). Serum immunoreactive parathyroid hormone (iPTH) was measured as the intact molecule by IRMA (Nichols, San Juan Capistrano, CA).

## Data Handling and Statistical Analysis

The primary outcome measures were the usual pharmacokinetic variables, area under the curve (AUC), both at five hours and at 24 hours (for both total and ionized serum calcium), as well as the time of maximum serum concentration (Tmax) and the magnitude of the elevation (Cmax). AUC was calculated by the trapezoidal method, and Cmax and Tmax were analyzed both by taking the observed values for concentration and time and by fitting the means of the timed serum increments for each source, using a first-order, two-compartment model with an absorptive delay of 0.5 hours (PKAntilyst; Micro-Math Scientific Software, Salt Lake City, Utah). The curves were plotted, and the phamacokinetic parameters were calculated, both as the absolute values and as the increment above baseline. Secondary variables were serum iPTH and urine calcium, the latter with and without adjustment for urine sodium. AUC for IPTH was calculated using the same approach as for serum calcium. The sodium adjustment was made in two ways, using a slope factor of either $0.004 \mathrm{mg} \mathrm{Ca} / \mathrm{mEq}$ sodium or $0.010 \mathrm{mg} \mathrm{Ca} / \mathrm{mEq} \mathrm{Na}$. In each case adjuṣ!ment was to the mean sodium excretion value for a given calcium source. The first factor is in the middle of the range reported in the literanure for the relationship of urine calcium and sodium [11,12]. The second factor was derived from the slope of urine calcium to urine sodium observed with the blank meal in the subjects of this investigation. For the test calcium sources, urine calcium values are reported as the increment above the calcium content of the corresponding collections obtained on the test day with the blank load.

A standard bioequivalence analysis [13] was performed both on serum total and serum ionized calcium, using AUC from 0 to 5 and 0 to 24 hours, as well as Cmax and Tmax. AUC for serum PTH was also compared. Only the data from the first three periods were used in these bioequivalence analyses, since the treatment in the fourth period (non-pharmaceutical calcium carbonate) was not in random order. A general linear model was fit with the natural logarithm of the variate as the dependent variable, test source, sequence, period and subject nested
in sequence as factors and the pre-dose value of the parameter as a covariate. The test sources in this equivalence analysis were Os-Cal@, Cirracal@ and blank. The sequence (or order) effect was tested using the subject in sequence mean square as the error term. The adjusted mean difference between the carbonate and citrate sources was computed and its $90 \%$ and 99\% confidence intervals were constructed. The difference and the bounds of the confidence interval were exponentiated to obtain the ratio of the carbonate source mean to the citrate source mean and its confidence interval. As set forth in the applicable FDA Guidelines [13], if the confidence interval for the ratio fell in the range from 0.80 to 1.25 , bioequivalence was considered to have been demonstrated.

Cmax and $T \max$ were compared between treatment groups using paired $t$ tests. Pharmacokinetic parameters for Os-Cal(B) and Citracal@ were each compared to blank using linear contrasts in the general linear model described above. Pharmacokinetic parameters for Os - $\mathrm{Cal}(8)$ and $\mathrm{Citracal}(8)$ were each compared to $\mathrm{CaCO}_{3}$ using paired $t$ tests. Changes from pre-dose serum concentrations of total and ionized calcium were compared among ireatment groups at each time point using doublyrepeated measures ANOVA. Each pairwise comparison among test sources was tested and type I error was controlled at the $5 \%$ level using Holm's step-down method. Urine calcium and sodium-adjusted urine calcium were compared between calcium sources using paired $t$ tests. AUC values for incremental calcium and PIH ratio to baseline were correlated by standard Pearsonian regression. All of these analyses used within-subject differences to make inferences concerning the pharmacokinetic parameters, and in this way full adjustment was made for between-subject differences in absorptive efficiency.

To determine the cost of these supplements, we used the average price at all US outlets and also calculated separately the mass market costs/g of elemental calcium for $\mathrm{Os}-\mathrm{Cal}$ and for Citracal@ between April and September 30, 2000. The data are provided by AC Nielson. The savings associated with hip fracture reduction were based on a previous analysis of this issue [4] for calcium supplements generally, which in turn used the average 1995 cost per discharged patient with a hip fracture, the size of the age cohort concerned and the fractional reduction in risk derived from published trials of calcium supplementation.

## RESULTS

Table 1 presents the pharmacokinetic parameters for both total and ionized serum calcium for the four test sources, and Fig. 1 and 2 show the time courses of total and ionized calcium, respectively. The AUC values for the three calcium sources were ail highly significantly different from the blank ( $p<$ 0.001 ), but there was no significant difference between the three calcium-containing sources for either of the AUC values

Table 1. Serum Calcium Pharmacokinetic Parameters (Mean $\pm$ SEM)

| $\frac{\text { Parameter }}{\text { Total } \mathrm{Ca}}$ | $\begin{gathered} \text { Os-Cal } \\ n=24 \end{gathered}$ | Citracal $n<24$ | $\begin{aligned} & \mathrm{CaCO}_{3} \\ & \mathrm{n}=23 \end{aligned}$ | $\begin{gathered} \text { Blank } \\ n=24 \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: |
| Increment $\mathrm{AUC}_{5}$ | $1.81 \pm 0.22$ |  |  |  |
| Increment AUC ${ }_{24}$ | $6.69 \pm 1.07$ | $1.88 \pm 0.18$ $5.91 \pm 1.02$ | $1.95 \pm 0.15$ | $0.04 \pm 0.14$ |
| Cmax | $10.3 \pm 0.07$ | $10.3 \pm 0.08$ | $6.39 \pm 0.85$ | $-0.05 \pm 0.77$ |
| Tmax | $4.8 \pm 0.5 \mathrm{~L}$ | 10.3 $4.2 \pm 0.36$ | $10.3 \pm 0.07$ | - |
| Ionized Ca |  | $4.2 \pm 0.36$ | $4.1 \pm 0.32$ | - |
| Increment $\mathrm{AUC}_{5}$ | $0.83 \pm 0.11$ | $1.02 \pm 0.11$ |  |  |
| Increment $\mathrm{AUC}_{24}$ | $2.36 \pm 0.56$ | $3.58 \pm 0.53$ | $0.85 \pm 0.10$ | $-0.05 \pm 0.09$ |
| ${ }_{\text {Cmax }}$ | $5.3 \pm 0.02$ | $5.4 \pm 0.03$ | $2.58 \pm 0.46$ 53 | $0.47 \pm 0.56$ |
|  | $5.1 \pm 0.91$ | $4.3 \pm 0.43$ | $3.1 \pm 0.26$ | - |

or any of the other pharmacokinetic parameters. Also, as Fig. shows graphically, the three sources produced virtually identical toral serum calcium time courses, whether expressed as absolute values (Fig. 1A) or as increxnent above baseline (Fig. 1B). Serum calcium values differed significantly from the corresponding values following the blank load at all time points from 3 to 12 hours for Os -Cal@ and from 1 to 9 hours for Citracal 8 , but there were no significant differences between the calcium sources at any time point. Fig. 2B shows that the incremental elevation of serum ionized calcium for the citrate source was somewhat greater from 5 to 12 hours compared to Os -Cal(6) and from 5 to 9 hours compared to the plain calcium carbonate. Consistent with this difference, the AUC $_{24}$ for ionized calcium (Table 1) was greater for the citrate than for the carbonate preparations. However, given the dispersion of the individual AUC data, none of these differences was statistically significant. There was no effect of the order of the test substance on any of the outcome variables. Similarly, age and estrogen status were also tested and were without effect on the relative absorbabilities of the test calcium sources.

Standard bioequivalence analysis of AUC and Cmax indicated that the carbonate and citrate test sources were bioequiva lent with respect to serum total and ionized calcium (Table 2). In fact, for all paramerers, the ratio of the values for the two sources differed from unity by less than $1 \%$. Both the carbonate and cirrate test sources were significantly different from blank: with respect to AUC and Cmax for serum total and ionized calcium. There was no evidence of a difference between the Os-Cal@ and $\mathrm{CaCO}_{3}$ or between Citracal ${ }^{(1)}$ and $\mathrm{CaCO}_{3}$ with respect to AUC, Cmax, or Tmax for serum total and ionized calcium, with one partial exception. The time to peak concentration was approximately one hour later with the Citracal (0) tes! source than with the $\mathrm{CaCO}_{3}$ test source ( $p<0.05$ ) when using the measured data. Using the mean data fitted to a pharmacokinetic model (a probably better approach), no significant differences were found between the Tmax estimates for any of the sources.

Fig. 3 presents the serum IPTH values for all four sources, first as absolute values (A), then as fractions of the baseline value (B). As is evident, depressions for the three calcium sources were virtually identical, amounting to a drop of $-40 \%$ at three hours after calcium ingestion. The $A \cup C_{24}$ values for iPTH (not shown) did not differ among the calcium sources, but all three sources did differ significantly from the blank. For both of the carbonate sources (data not shown), but not for the citrate, $\mathrm{AUC}_{24}$ for the iPTH decrement from baseline was significandy correlated with $\mathrm{AUC}_{24}$ for incremental $\left[\mathrm{Ca}^{2+}\right]$ ( $p<0.001$ ) .

Table 3 presents the urine calcium increments for the three calcium-containing sources above the corresponding urine calcium excretion values for the blank load. Both from 0 to 5 hours and from 5 to 24 hours, the wine calcium increments differed significantly from zero for all three sources. The citrate produced a $\sim 40 \%$ greater rise in urine calcium from 5 to 24 hours than either of the carbonate preparations, but, given the wide dispersion of individual values, the difference between sources was not significant. Calcium and sodium excretion were significantly correlated in our subjects as expected (data not shown), and both methods of correcting for sodium excretion slightly reduced the dispersion of the urine calcium values. Nevertheless, the sodium-corrected values, like the uncorrected, did not differ significantly between calcium sources.

The costs of the two supplements and cost:benefit analyses are presented in Table 4. Columns 4 and 8 contain the net benefit of supplementation (in dollars per capita for the population treated). A positive value means that the savings exceed the cost, while a negative value means a net cost. (A negative value is not necessarily bad, since prevention of most diseases usually carries a net cost. Thus the principal value of the net benefit figure is to facilitate comparison between sources.) The citrate source we tested costs between 1.5 and 1.8 times as much as the carbonate source, per gram of elemental calcium. Provision of the carbonate product to all US women 75 years of age and older for 2.83 years was projected to be cost effective,



Fig. 1. Time course of the total serum calcium, both as absolute values (A) and as increment above baseline (B), for the three calcium sources and for the blank load. Error bars are 1 SEM. (Copyright Roben P. Heaney, 2000. Used with permission.)
saving $\$ 100$ million in hip-fracture associated, costs/year; by contrast, the cirrate source was not cost effective. If increasedbone mineral density is assumed to be predictive of hip fracture reduction, then universal supplementation of all men and women aged 65 years and older remains cost effective using the


Flg. 2. Tirne course of the ionized serum calcium increment above baseline for the three calcium sources and for the blark load, boch as absolute values (A) and as increment above baseline (B), for the three calcium sources and for the blank load. Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)
carbonate as the calcium source; the net potential benefit is $\$ 478$ million/year or a per capita benefit of $\$ 14.26$. It is worth noting that the annual cost for providing 1000 mg of elemental calcium as the carbonate preparation is less than $\$ 70$ per person.

Table 2. Bioequivalence Analysis

| Parameter | Ratio: Os-Cal to Citracal | 90\% CI | $99 \% \mathrm{Cl}$ | Conclusion* |
| :---: | :---: | :---: | :---: | :---: |
| Total Ca $\mathrm{AUC}_{3}$ | 0.999 |  |  |  |
| Total Ca AUC 24 | 1.004 | $0.990,1.007$ $0.995,1.012$ | $0.985,1.013$ $0.990,1.018$ | bioequivalent |
| Total Ca Cmax | 1.003 | 0.991, 1.014 |  | bioequivalent |
| Yonized $\mathrm{Ca} \mathrm{AUC}_{5}$ | 0.994 | 0.985, 1.002 | 0.984, 1.021 | bioequivalent |
| Ionized $\mathrm{Ca} \mathrm{AUC}_{24}$ | 0.992 | 0.986, 0.998 | 0.980, 1.008 | bicequivalent |
| Ionized Ca Cmax | 0.995 | 0.984, 1.006 | 0.977, 1.012 | bioequivalent bioequivalent |

* Bioequivalence is concluded if the $90 \%$ confidence interval falls besween $0 . k 0$ and 1.25 . The analysis was perfonmed on log-transformed data, and the difference between exponentiated for the upper and lower bounds on the ratio presented in the table.


Fig. 3. Time course of serum iPTH following ingestion of the three calcium sources and for the blank load, both as absolute values ( A ) and as fractional values relative to baseline (B). Error bars are 1 SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)

## DISCUSSION

Calcium supplementation has been shown, in well-controlled clinical studies, to slow age-related bone loss and reduce the risk of hip and other fractures in middle aged and older men and women. Using U.S. data on the medical costs associated with hip fracture compared to the costs of preventive supplementation with calcium, Bendich et al. found that supplemen-
tation targeted at those at greatest risk could save over $\$ 2.5$ billion/year [4]. However, cost-effectiveness of calcium supplementation depends not only on the cost of the product, but on the efficiency of its absorption. All published cost-benefit analyses to date have assumed not only an average price per gram of calcium regardless of the salt, but equal bioavailability for all calcium sources.

Shangraw [14] had previously shown marked differences in dissolution of calcium supplement preparations, due solely to phanmaceutical formulation differences, and unpublished experience of one of us (RPH) has demonstrated that not all preparations of the same salt exhibit equivalent absorbability. Finally, Heller et al. [7] explicitly raised this question in their recent paper. It is reassuring, therefore, to note that, in this study, Os-Cal ${ }^{(1)}$ and the non-pharmaceutic, precipitated calcium carbonate exhibited identical bioavailability values. Thus for at least one marketed calcium carbonate product, pharmacentical formulation does not alter the intrinsic bioavailability of its calcium salt. The came conclupion in probably applicablo to the marketed citrate product as well. This is because it did not differ from non-pharmaceutic calcium carbonate in this study and because we had previously shown that the bioavailability values of the pure carbonate and citrate salts wére identical [8].

Interestingly, however, and not previously described. several small differences were noted in pattern of response between the citrate and carbonate sources. None was statistically significant in isolation, but taken together, their mutual consistency suggests underlying differences in metabolic response to the two salts. These effects were i) although the rise in total calcium was the same, slightly less of the increment in serum calcium following the carbonate products was carried as the ionized form and slightly more as the bound form, relarive to the citrate salt; ii) PTH suppression was slightly greater for the Citracal (8) than for the Os-Cal@, and the difference approximately coincided with the time points at which the ionized calcium differences were most prominent; and iii) urine calciurn excretion in the 5 to 24 hour pool was higher for the Citracal ${ }^{2}$ than for $\mathrm{Os}-\mathrm{CalQ}$. The relative depression is shown most clearly in Fig. 4, which plots ionized calcium as a percent of total calcium and shows slightly lower values for the OsCal from 5 to 9 hours. This relative depression may reflect a very slight degree of alkalosis due to exhalation of $\mathrm{CO}_{2}$ from the carbonate anion, but the reason for the delay after ingestion

Table 3. Urine Calcium Increments after Ingestion of Test Calcium Sources*

|  | $0-5$ hours |  |  | 5-24 hours |  |  | 0-24 hours |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | N | Mean | SEM | N | Mean | SEM | N | Mean | SEM |
| Os-Cal | 23 | 21 | 3 | 22 |  |  |  | Mean | SEM |
| Citracal | 23 | 16 | 3 | 22 | 32 |  | 22 | 43 | 10 |
| $\mathrm{CaCO}^{3}$ | 21 | 20 | 4 | 20 | 30 | 10 | 22 | 45 | 9 |
|  |  |  |  | 20 | 20 | 10 | 20 | 38 | 9 |

Table 4. Cost: Benefit Aarlysis of Two Calcium Supplements

|  | No. of tabs per boule | Men add wullen aged $\sim 05$ years$(\mathrm{n}=33,540 ; 000)$ |  |  |  | Women aged $\geq 75$ years$(\mathrm{a}=9,426,000)$ |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Cost per person 1 year (\$) <br> (I) | Cost for 1 year (\$ million) <br> (2) | Net benefit (\$ million) (3) | Net <br> per-capita benefit (\$) <br> (4) | Cost per person 2.83 year (\$) (5) | Cost for 2.83 year (\$ million) (6) | Net <br> benefit <br> (\$ million) <br> (7) | Net per-capita benefit (\$) |
| Os-Cal $500 \mathrm{mp} \mathrm{Ca}+200 \mathrm{TOD}$ | 75 160 | 68.62 | 2,302 | 140 | 4.18 | 194.20 |  |  | (8) |
| Citracal 200 mg Ca | 160 | 58.54 | 1,963 | 478 | 14.26 | 165.67 | 1,831 | -169 | -17.88 |
| Citracal 200 mg Ca | 200 | 86.69 | 2,907 | -466 | -13.89 | 245.34 | 1,562 | 100 | 10.65 |
| Citracal $315 \mathrm{mg} \mathrm{Ca}+200 \mathrm{MUD}$ | 100 | 116.25 | 3,899 | -1,457 | -43.45 | 329.01 | 2,313 3,101 | -651 | -69.02 |
| Citracal $315 \mathrm{mg} \mathrm{Ca}+200 \mathrm{IU} \mathrm{D}$ | 120 | 123.02 | 4,126 | -1,684 | -50.22 | 348.16 | ,1 | 1439 | -152.69 |
| is the estima |  | 92.02 | 3,086 | -645 | -19.22 | 260.44 | 2,455 | -1620 -793 | -171.84 -84.12 |

(1) Mos apuarion sizo.
(2) Cost for one year's supply for this population $(\mathbb{N} \times(1))$.
(3) Prevencall 1
(4) Net benefit divided by the popalation size ( $(3) \div N$ ).
(5) Mass marict cost (AC Niepor
(6) Cost for 2.83 years' supply for this population ( $\mathrm{N} \times$ ( S ) . .
(7) Prever 2.83 years supply for this population ( $\mathrm{N} \times(5)$ ).
(7) Preventable total expendiures $(\$ 1,662$ million for 1995 in this population) minus the cost of supplying the entire population for 2.83 years ( 6 ).
(8) Net benefit divided by the population $((7) \div \mathrm{N})$.

NB: Calculations based by the population $((7) \div \mathrm{N})$.
NB: Calculations based
Supp (revised $3 / 5 / 01$ )
is unclear. Physiologically, these changes are mutually consistent, since a higher ionized calcium would be expected to lead to a greater depression of PTH release, to an increased filtered calcium load at the kidney and, through lowered PTII, to decreased tubular reabsorption of calcium. Although the greater rise in urine calcium with calcium citrate was not statistically significant in this study, it is worth noting that Heller et al. [7] reported a significant loss of calcium in urine following supplementation with calcium citrate (Citracal(1)) which was not seen with an equivalent dose of calcium carbonate ( $\mathrm{Os}-\mathrm{CaI}(\mathrm{B}$ ).

We had not designed the study to evaluate this issue, and, indeed, we had not anticipated it. Neverheless, it is worth noting that the finding of a slight increase in calcium excretion with the citrate source is consistent with what we had reportcd previously [8]. In that earlier investigation, despite identical tracer-based absorption fractions for the cirrate and carbonate salts of calcium, there was a tendency for the urine calcium increment to be greater with the citrate than with the carbonate. We had atrributed that finding to a calciuric effect of absorbed cirrate, but, in view of the ionized calcium findings in this study, it may, instead, reflect a mild alkalotic effect of the carbonate salt.

On a methodologic note, it may be worth mentioning that the increments in urine calcium were substantially more variable than the increments in serum calcium. The coefficients of variation (CVs) of the serum and urine calcium increments at their peak values ( 3 and 5 hours for serum and 0 to 5 hours for urine), for all calcium sources, were $38 \%$ to $60 \%$ for serum and $77 \%$ to $99 \%$ for urine. This roughly twofold greater variability underscores, as we have noted previously [8], the relative
weakness of using the rise in urine calcium to estimate absorptive performance, particularly for loads as small as 500 mg .

For this study, the retail cost per 1000 mg of ingested calcium was between $\$ 0.16$ and $\$ 0.20$ for the marketed calcium carbonate product and between $\$ 0.24$ and $\$ 0.38$ for the marketed calcium citrate product. Since both sources exhibited equivalent bioavailability, it is clear that the carbonate source was the less expensive of the two per unit of absorbed calcium and would therefore exhibit a more favorable cost-benefit relationship in a cost-effectiveness analyses such as set forth in Table 4. Additionally, although not usually considered in cost benefit analysis, the greater calcium density of carbonate-based


Fig. 4. Time course of serum ionized calcium expressed as a percent of total serum calcium for the three calcium sources. Etror bars are I SEM. (Copyright Robert P. Heaney, 2000. Used with permission.)
products means that fewer pills are needed to achieve a desired supplement intake, a factor known to influence patient compliance [15].

In this study we used $2 S(\mathrm{OH}) \mathrm{D}$ as a rapid and efficient means of ensuring approximately equivalent vitamin $D$ status in all subjects. Such treatment would nat be a part of popula-tion-level supplementation, and its costs are, accordingly, not a part of our calculations. Vitamin $D$ is contained in both of the supplements tested here, and its cost is, therefore, alrendy factored into the analysis summarized in Table 4.

While we tested only two commercially available products in this analysis, our purpose was not so much to contrast these two specifically as to use them as examples for a type of calculation and analysis that should be performed for all marketed calcium supplement products. It was beyond the scope of this project to underake an exhaustive survey of different pharmaceutical formulations, although we believe this should be done. It is a matter of commonplace experience that there are many other calcium products available, at least some of which explicitly meet the USP disintegration and dissolntion standards for calcium supplements (and therefore can be presumed to have a bioavailability comparable to what we found here). Their prices range from as low as $\$ 0.09$ per 1000 mg to as much as $\$ 0.53$. Lacking bioavailability data for most of these products, it is uncertain whether any of them would exhibit an advantage over the products tested here.

In conchusion, based upon bioavailability, cost and clinical efficacy, calcium carbonate, in the form of $\mathrm{Os}-\mathrm{Cal}($, would appear to be a good choice for calcium supplementation in a US population at risk for both low bone mineral density and hip fracture.

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# Absorbability and Cost Effectiveness in Calcium Supplementation 

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Key pords: calcium absorption, calcium carbonate, calcium citrate, hioavailability, cost-effectiveness
 on the efficiency of its absorprion. Published coit-benefir analyses assume equal bioavailability for all calcium sources. Some published studies have suggested that there are differences in both the bioavailability and cost of the tajor calcium supplements.

Design: Randomized four period, three-way cross-over comparing simgle doses of off-the-shelf commerciai calcium supplements containing either calcium carbonate or calcium citrate compared with a no-load blank and with encapsulated calcium carbonate devoid of other ingredients; subjects rendered fully vitannin D-replete with $10 \mu \mathrm{~g} / \mathrm{day} \mathrm{SE}(\mathrm{OH}) \mathrm{D}$ by mouth, staring pne weak prior ta the first test.

Subjects: 24 posmenopausal women
Methods: Pbarmacokinedic analysis of the increment in scrum total and ionized colcium and the decrement in serum IPTH induced by an oral calcium load, based upon multiple blood samples over à 24 hour period; measurement of the rise in urine calcium excretion. Data analyzed by repeated measures ANOYA. Cost calcularions based on ayerage retril prices of marketed products used in this sudy from April through October, 2000.

Results: All three calcium sources (marketed calcium carbonate, encapsulated calcium carbonate and marketed calcium cirate) produced identical 24 -hour time courses for the increment in total serum calcium. Thus, these were equally absorbed and had equivalent bios agilability. Urine caicium rose slightly more with the citrate than with the captonate preparations, but the difference was nat significant. Serum IPTH showed the expected depression accompanying the rise in seram calcium, and there were no significant differences between prodicts.

Conctusion: Given tut equivalent biunvuilability of the two marketed products, the cost benefit analysis favors the leas expensive carboate proiuct.

## INTRODUCTION

There is general acceptance of the impoitance of achieving adequate calcium intakes throughout life, and in most adults effort in that regard means taking some form of colcium supplement. Over half the women enrolled in the Women's Health Initiative reported using supplements, and this figure rose to nearly $60 \%$ in women over age 70 [1]. While calcium supplementation has generally been considered a cost effective intervention $[2,4]$, much depends upon the cost of the preperation. Thus Torgerson and Kanis, in the UK, calculated that calcium

Was not cost effective for a preparation they priced at $\sim \$ 0.50 / \mathrm{g}$ in current dollars [5]. Lowering that cost modestly produced a more favorable relationship. Bendich, et all. [4] found that calcium supplementation at 1200 m dayy and a coss of wo 10$0.12 / \mathrm{g}$ was cost effective forraly US women 75 yeart of age or older whent calculated against the costs of care associated only with hip fracture. If the endpoint was increase in bone mineral density and its associated lower total fracture nisk, then calcium supplementation was cost effective even with universal supplementation of all US men and women 65 years of age or older.

An additional consideration, given virtually no attention to
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date, involves factoring in bioavailability of the calcium source. Most, if not all, andyses to date have assumed equivalent bioavailability for different salts and different consumer formularions. Recent publications by Heller et aL [6,7] suggestid that this might not be the case. The authors xeported absorbability for a calcium citrate supplement superior to that of a commercially marketed calcium carbonate product. Since the rwo salts, in pure form, had been shown in several studies to be absorbed equally well [ $8-10$ ], a question arose as to whether differences in pharmaceutical preparacion of marketed products might have interiered with or enbanced the nbsorbability of one or the other preparation. Such absorptive effects, if they exist. would alter cost effectiveness calcuiations, once calcium acrually delivered into the blood stream becomes the basis for the computation.

Accordingly we set out to compare two commercial supplcments, using standard pharmacokinetic methods, both with one another and with non-pharmaceutical calcium cartonate int gested without excipients. This communication describes the results of this investigation. Additionally, we then used the bioavailability data to calculate the costs associated with providing the two commercially available calcium salts to the US population at greatest risk of hip fracture.

## MATERTALS AND MRTPIODS

## Subjects

Subjects were 24 postmenopausal women aged $56.1 \pm 7.1$ years and in good general health. Their BMI was $29.3 \pm 5.7$ $\mathrm{kg} / \mathrm{m}^{2}$. Thirteen subjects were receiving estrogen replacement therapy, and the remaining 11 were not. One was AfricanAmerican; the others were Caucasian. Subjects taking calciunn supplements were asked to abstain throughout the course of the study, starting at least one week in advance of the first test. Additionally, subjects were counseled by our research dietilian to hold calcium from dietary sources to under 400 mp/day. mainly by avoiding all dairy products. Also, they were instructed to avoid high sodium foods (such as commercial fast foods and canned soups or soup mixes) starting two days prior to and including each test day. To eliminate any variability in absorptive performance due to vitamin $D$ insufficiency or to seasonal change in vitamin $D$ status, all subjects were given 10 $\mu \mathrm{g} 25(\mathrm{OH}) D_{3}$ (Calderol ${ }^{(1)}$, Organon, West Orange, NJ$) /$ day starting one week before the first test and continuing throughout the study. This dose is approximately equivalent to 1000 IU ( $25 \mu \mathrm{~g}$ ) of cholecalciferol, but produces a rapid elevacion of serum $25(\mathrm{OH}) \mathrm{D}$, in contrast with the five month time-io-equilibriun required when using cholecalciferol. Further, this ciose is the amount required, at Omaha's latitude, to bring serum 25 (OL) D concentration up to $32 \mathrm{ag} / \mathrm{nL}$ ( $80 \mathrm{nmol} / \mathrm{L}$ ), a level widely considered to be the lower limit of physiologicul normal. The study was approved by the Creightom Universisy

Institutional Review Board, and each subject gave written consent.

## Design

The sudy was a four-perior, three-way raidomized crossover, within-subject design, with each individual receiving Os-Cal(o (a product manufactured by GlaxoSmithKline and consigting of calcium carbonate derived from oyster shell), Citracal (a) (a product manufacured by Mission Pharmacal and consisting of calcium citrate), a gelatin capsule containing precipitated calciun carbonate or an empty gelatin capsule (the blank). The test source was ingested midway through a standard light breakfast containing two pieces of Italian-style white bread (Center-baked from anenriched flour), toasted and buttered, together with a cup of coffee, tea or water (with arificial sweetener if desired), plus additional water to ensure adequate urine volume. Blood samples were taken at $0,1,3,5,7,9,12$, and 24 hours for measurement of total and ionized calcium and parathyroid hormone (PIH). Urine was collected in two pools, from 0 to 5 hours, and from 5 to 24 hours, and was analyzed for calcinm, creatione and sodium. Calcium sources were given only on the test day and only at the breakfast meal. The noou meal was provided by Center staff between the 5 and 7 hour blood draws and was designed to be Iow in both calcium and sodium. The evening meal was ingested between the 9 and 12 hour blood draws. Tests were separated typically by seven days; in this way the entire suite of studies was completed for most subjects within a 22 -day period so as to minimize temporal variability in absorptive performance.

## Test Sources

For the two commercial products ( $\mathrm{Os}-\mathrm{Cal}(\mathrm{B}$ and Ciracal (®), the sources were purchased from a retail phamacy. The labeled content of eiemental calcium for the Os-Cal回 was 500 mg , plus 200 I.U. of vitamin $D$ (Control No. 9K2228; exp. date 11/D1). In order to approximate the load size of the OS-CalQ, the Citracalg dose required a combination of two different formulations, one labeled to contain 200 mg elemental calcium (Lot 9D12; exp. date 4/02) and the ather 315 mg plus 200 I.IU. vitamin D (Lot 9E86; exp. date 5/01). Precipitated calcium carbonate was prepared in the Center's laboratory by dissoiving reagent grade calcium chloride in distilled water, heating to $80^{\circ} \mathrm{C}$ with stirring and adding a slight stoichiometric excess of a heated aqueous solution of sodium carbonate, timed so that the reaction was completed within one minute. The resulting precipitate was collected on a fritted glass Ellter, washed widh deionized water to remove adsorbed sodium chloride, dried at $90^{\circ} \mathrm{C}$ overnight, ground in a mortar and packed loosely into tared gelatin capsules in sufficient quantiny to provide a 500 mg calcium load per dose. All preparations were chemically analyzed; actual ingested loads of. calcium were as follows: for Os-Cal(0), 503 mg ; for Citacale, 516 mg , and for precipitatec calcium carbonate, 497 mg .

## Analytical Methods

Calcium in senm，urine and the ingested sources was ana－ lyzed by atomic absorption spectrophotometry（AAnaiyst 100， Perkin－Elmer，Norwalk，CT），creatinine in mine by an auto analyzer method（Chinun Enpress Plis，Coba Conjing Diagnos－ tics，Medfeld，MA）and sodium in urine by an ion selective electrode method（Cobas Integra，Roche Diagnostics，Basel， Switzerland）．Serum ionized calcium was analyzed under stan－ dardized test conditions by an ion selective electrode method （Nova Nucleus，Nova Biomedical，Waltham，MA）．Serum im－ munoreactive parathyroid homone（iPTH）pas measured as the intact molecule by IRMA Nichols，San Juan Capistrano， CA）．

## Data Handling and Statistical Analysis

The primary outcome measures were the usual pharmaco－ binetic variables，area under the curve（AUC），both at five hours and at 24 hours（for both total and ionized sermm calci－ um），as well as the time of meximum serum concentration （Tmax）and the mingitude of the elevation（Cmar）．AUC was calculated by the trapezoidal merhod，and Cmax and Tmax were analyzed both by taking the observed values for concen－ tration and time and by fitting the means of the timed serum increments for each source，using a Eirst－order，two－compart－ ment model with an absorptive delay of 0.5 hours（PKAntilyst； Micro－Math Scientific Softrare，Salt Iake City，Utah）．The curves were plotted，and the phammacolinetic parameters were calculated，both as the absolute values and as the increment above baseline．Secondary variables were serum iPTH and urine calcium，the latter with and without adjustment for wrine sodiun．AUC for IPTH was calculated using the same approach as for serum calcium．The sodium adjustment was mand in two ways，using a slope factor of either $0.004 \mathrm{mg} \mathrm{Ca} / \mathrm{mEq}$ sodium or $0.010 \mathrm{mg} \mathrm{Ca} / \mathrm{mEq}$ Na．In ench case adjustment．was to the mean sodium excretion value for a given calcium source．The first factor is in the midale of the range reported in the literabure for the relationship of urine calcium and sodium［11，12］．The second factor was derived from the slope of urine calcium to urine sodium observed with the blank meal in the subjects of this investigation．For the test caicium sources，urine calvium values are reported as the increment above the calcium content of the corresponding collecrions obtained on the test day with the blank load．

A standard bioequivalence analysis［13］was performed both on serum total and serum jonized calcium，using AUC from 0 to 5 and 0 to 24 hours，as well as Cmax and Tman．AUC for semm PIH was also compared．Only the data from the first three peniods were used in these bioequivalence analyses，since the treatment in the fourth period（non－phamaceutical calcium carbonate）was not in random order．A general linear model was fit with the natural logarithm of the variate as the depen－ dent variable，test source，sequence，period and subject aested
in sequence as factors and the pre－dose value of the parameter as a covariate．The test sources in this equivalence analysis were Os－Cal＠，Cirracal昌 and blank The sequence（or order） effect was tested using the subject in sequence mean square as the error term．The adjusted mean difference between the carbonate and citrate sources was computed and its $90 \%$ and $99 \%$ confidence intervals were constructed．The difference and the bounds of the confidence interyal were exponentiated to obtain the ratio of the carbonate source mean to the citrate source mean and its confidence interval．As set forth in the applicable FDA Guidelines［13］，if the confidence interval for the ratio fell in the range from 0.80 to 1.25 ，bicequivalence was considered to have been demonstrated．

Cmax and Tmax were compared between treatment groups using paired $t$ tests．Pharmacokinetic parameters for Os－Cai＠ and Citracal（8）were each compared to blank using linear con－ trasts in the general linear model described above．Pharmaco－ kinetic parameters for $\mathrm{Os}-\mathrm{Cal} 8$ and $\mathrm{Citracal} ⿴ 囗 十 介$ were each com－ pared to $\mathrm{CaCO}_{3}$ using paired $\pm$ tests．Changes from pre－dose serum concentrations of total and ionized calcium were com－ pared among treatment groups at each time point using doubly－ repeated measures ANOVA．Each pairwise comparison among test sources was tested and type I error was conmolled at the $5 \%$ level using Holm＇s step－down method．Urine calcium and sodium－adjusted urine calcium were compared between cal－ cium sources using paired f tests．AUC values for incremental calcium and PIH ratio to baseline were correlated by standard Pearsonian regression．All of these analyses used within－sub－ ject differences to make inferences coneerning the pharmaco－ kinetic parameters，and in this way full adjustment was made for between－subject differences in absorptive efficiency．

To determine the cost of these supplements，we used the ayerage price at all US outlets and also calculated separately the mass market costs／g of elemental calcium for $\mathrm{Os}-\mathrm{Cal}$ and for Citracal＠between April and September 30，2000．The data are provided by AC Nielson．The savings associated with hip fracture reduction were based on a previous anslysis of this issue［4］for calcium supplements generally，which in turn used the average 1995 cost per discharged patient with a hip fiacture， the size of the age cohort concermed and the fractional reduc－ tion in risk derived from published trials of calcium supple－ mentation．

## RESULTS

Table 1 presents the pharmacokinetic parameters for both total and ionized serum calcium for the four test sources，and Fig． 1 and 2 show the time courses of total and ionized calcium， respectively．The AUC values for the three calcium sources were all highly significantly different from the blank（ $p<$ 0.001 ），but there was no significant difference between the three calcium－containing sources for either of the AUC values

Table 1. Sermen Colicium Phannacokinetic Parmeters (Mean 土 SEM)

| Parametar | $\begin{aligned} & \mathrm{O}_{5}-\mathrm{Cal}^{2} \\ & \mathrm{n}=24 \end{aligned}$ | Citracal $n \div 24$ | $\begin{aligned} & \mathrm{CaCO}_{3} \\ & \mathrm{n}=23 \end{aligned}$ | Blank $n=24$ |
| :---: | :---: | :---: | :---: | :---: |
| Total Ca |  |  |  |  |
| Incremeni $\mathrm{AUC}_{5}$ | $1.81 \pm 0.22$ | $1.88 \pm 0.18$ | $1.95 \pm 0.15$ | 0.04 $\pm 0.14$ |
| Increment $\mathrm{AUVC}_{24}$ | $6.69 \pm 1.07$ | $5.91 \pm 1.02$ | $6.39 \pm 0.85$ | $-0.05 \pm 0.77$ |
| Cmax | $10.3 \pm 0.07$ | $10.3 \pm 0.08$ | $10.3 \pm 0.07$ | $\sim$ |
| Tmax | $4.8 \pm 0.51$ | $4.2 \pm 0.36$ | $4.1 \pm 0.32$ | - |
| Ionized Ca |  |  |  |  |
| Increment $\mathrm{AUC}_{5}$ | $0.83 \pm 0.11$ | $1.02 \pm 0.11$ | $0.85 \pm 0.10$ | $-0.05 \pm 0.09$ |
| Increment $\mathrm{AUC}_{24}$ | $2.36 \pm 0.56$ | $3.58 \pm 0.53$ | $2.58 \pm 0.46$ | $0.4 T \pm 0.56$ |
| Cmax | $5.3 \pm 0.02$ | $5.4 \pm 0.03$ | $5.3 \pm 0.03$ | - |
| Tmax | $5.1 \pm 0.91$ | $4.3 \pm 0.43$ | $3.1 \pm 0.26$ | - |

ANC is measiured in mgfll $\cdot$ hour, Cusax is measured in mafdl, Imax is measured in hours.

Or any of the other pharmacokinetic paramerers. Also, as Fig. I shows graphically, the three sources produced virtually identical total serum calcium time courses, whether expressed as absolute values (Fig. 1A) or as increment above baseline (Fig. 1B). Senum calcium values differed significantly from the corresponding values following the blank load at all time points from 3 to 12 hours for Os-Cal@ and from 1 to 9 hours for Citracal@, but there were no significant differences between the calcinm sources at any time point. Fig. 2B shows that the incremental elevation of serum ionized calcium for the citrate source was somewhat greater from 5 to 12 hours compared is Os-Calcla and from 5 to 9 hours compared to the plain calciun carbonate. Consistent with this difference, the AUC $_{24}$ for ionized calcium (Table 1) was greater for the citrate than for the carbonate preparations. However, given the dispersion of the individual AUC data, none of these differences was statistically significant. There pas no effect of the order of the test substance on any of the outcome variables. Similarly, age and estrogen status were also tested and were without effect on tho relative absorbabilities of the test calcium sources.

Standard bioequivalence analysis of AUC and Cmax indicated that the carbonate and citrate test sonrees were bioequiva. lent with respect to serum total and ionized calcium (Table 2). In fact, for all paramerers, the ratio of the values for the cwo sources differed from unity by less than $1 \%$. Both the carbonate and citrate test sources were significantly different from blank: with respect to AUC and Cmax for serum total and ionized calcium. There was no evirience of a difference between the. Os-Cal@ and $\mathrm{CaCO}_{3}$ or between Citracal@ and $\mathrm{CaCO}_{3}$ with respect to ADC, Cmax, or Tmax for serum total and ionized culcinm, with one partial exception. The time to peak concentration was approximately one hour later with the Citracall test source than with the $\mathrm{CaCO}_{3}$ test source $(p<0.05)$ when using the measured data. Using the mean data Eirted to a phormacokinetic model (a probably better approach), no significant differences were found between the Tmax estimates for any of the sources.

Fig. 3 presents the serum IPTH values for all four sources, first as absolute values (A), then as fractions of the baseline value ( $B$ ). As is evident, depressions for the three calcium sources were virtually identical, amounting to a drop of $-40 \%$ at three hours after calcium ingestion. The $\mathrm{AUC}_{21}$ values for iPTH (not shown) did not differ among the calcinm sources, but all three sources did differ significantly from the blank. For both of the carbonate sources (data not shown), but not for the citrate, $\mathrm{AUC}_{24}$ for the IPTH decrement from baseline was significandly correlated with $\mathrm{AUC}_{24}$ for incremental $\left[\mathrm{Ca}^{2+}\right]$ ( $p<0.001$ ).

Table 3 presents the urine calcium increments for the three calcium-containing sources above the corresponding urine calcium excretion values for the blank load. Both from 0 to 5 hours and from 5 to 24 hours, the wine calcium increments differed significantly from zero for all three sources. The citrate produced a $\sim 40 \%$ greater rise in urine calcium from 5 to 24 hours than either of the carbonate preparations, but, given the wide dispersion of individual values, the difference between sources was not significant. Calcium and sodium excrecion were sigoificantly comelated in our subjects as expected (data not shown), and both methods of correcting for sodium excretion slightly reduced the dispersion of the urine calcium values. Nevertheless, the sodium-conrected values, like the uncorrected, did not differ significantly between calcium sources.

The costs of the two supplements and cost:benefit analyses are presented in Table 4. Columns 4 and 8 contsin the net benefit of supplementation (in dollars per capita for the population treated). A positive value means that the savings exceed the cost, while a negative value means a net cost. (A negative value is not necessarily bad, since prevention of most diseases usually carries a net cost. Thus the principal value of the net benefit figure is to facilitate comparison between sources.) The citrate source we tested costs between 1.5 and 1.8 times as manch as the carbonate soume, per gram of elemental calcium. Provision of the carbonate product to all US women 75 years of age and older for 2.83 years was projected to be cost effective,


Fig. 1. Time course of the total serum calcium, both as absolute walues (A) and as increment above baseline (B), for the three calciura nourters and for the blank load. Error bars are 1 SEM. (Copynight Robent P. Heaney, 2000. Used with permission.)
saving $\$ 100$ million in hip-fracture associated, costs/year; by contrast, the citrate source was not cost effective. If increasedbone mineral density is assumed to be predictive of hip fracture reduction, then universal supplementation of all men and women aged 65 years and older remains cost effective using the


Flg. 2 Time course of the ionized serum calcium increment above baseline for the three calcium sources and for the blark load, borh as absolute vaines $(A)$ and as increment above baseline ( $B$ ), for the three calcium sources and for the blank load. Error bars are 1 SEM. (Copy. right Robert P. Heaney, 2000. Used with pemission.)
carbonste as the calciun source; the net potential benefit is $\$ 478$ million/year or a per capita benefit of $\$ 14.26$. It is worth noting that the amual cost for providing 1000 mg of elemental calcium as the carbonate preparation is less than $\$ 70$ per person.

Table 2. Bicequivalence Analysis

| Parameter | Ratio: <br> Os-Cal to Citracal | 90\% CI | 99\% CI | Conclusion* |
| :---: | :---: | :---: | :---: | :---: |
| Total Ca AUC, | 0.999 | 0.990,1.007 | 0.985, 1.013 | bibequivalent |
| Total Ca $\mathrm{AUC}_{34}$ | 1.004 | 0.995, 1.012 | 0.990, 1.018 | bioequivalent |
| Total Ca Cmax | 1.003 | 0.991, 1.014 | 0.984, 1.021 | biocquivalent |
| Ionized $\mathrm{Ca} \mathrm{AUC}_{5}$ | 0.994 | 0.985, 1.002 | 0.980, 1.008 | bioequivalent |
| Ionized Ca $\mathrm{AVC}_{24}$ | 0.992 | 0.986, 0.998 | 0.982, 1.002 | bioequivalent: |
| Ioaized Ca Cmax | 0.995 | $0.984,1.006$ | 0.977.1.012 | bioequivalent |

[^2]

Fig. 3. Time course of serum iPIH following ingestion of the three calcium sources and for the blank load, both as absolute vilues $(A)$ and as fractional values relarive to baseline (B). Error bars are 1 SEM (Copyright Robert P. Heaney, 2000. Used with permission.)

## DISCUSSION

Calcium supplementation has been shown, in well-controlled clinical studies, to slow age-related bone loss and reduce the risk of hip and other fractures in middle aged and older men and women. Usiog U.S. date on the medical costs associated with hip fracture coropared to the costs of preventive supplementation with calcium, Bendich er al. found that supplemen-
tation targeted at those at greatest risk could save over $\$ 2.5$ billion/year [4]. However, cost-effectiveness of calcium supplementation depends not only on the cost of the product, but on the efficiency of its absomption. All published cost-benefit malyses to date have assumed not only an average price per gram of calcium regardless of the salh, but equal bioavailability for all calcium sources.

Shangraw [14] had previously shown marked differences in dissolution of calcium supplement preparations, due solely to pharmaceutical formulation differences, and unpublished experience of one of us (RPH) has demonstrated that not all preparations of the same salt exhibit equivalenr absorbability. Finally, Heller et al. [7] explicitly raised this question in their recent paper. It is reassuring, therefore, to note that, in this study, Os-Cal@ and the non-pharmaceutic, precipitated calcium carbonate exhibited identical bioavailability values. Thus for at least one marketed colcium carbonate product, pharmacentical formulation does not alter the intrinsic bioavailability of its calcium salt. The came concludion is probably appliouble to the marketed citrate product as well. This is because it did not differ from non-pharmaceutic calcium carbonate in this study and because we had previously shown that the bioavailability values of the pare carbonate and cirrate salts were identical [8].

Interestingly, however, and not previously described. several small differences were noted in pattern of response between the citrate and carbonate sources. None was statistically signifieant in isolation, but taken together, their mutual consistency suggests underlying differences in metabolic response to the two salts. These effects were i) although the rise in toral caicium was the same, slightly less of the increment in serum calcium following the carbonate products was carried as the ionized form and slightly more as the bonad form, relative to the cirrate salt; ii) PTH suppression was slightly greater for the Citracal8 than for the Os -Cal8, and the difference approximately coincided with the time points at which the ionized calcium differences were most prominent; and iii) urine calciurn excrecion in the 5 to 24 hour pool was higher for the Citreal@ than for Os-Cal@s. The relative depression is shown most clearly in Fig. 4, which plots ionized calcium as a percent of total calcium and shows slightly lower values for the OsCal( from 5 to 9 hours. This relative depression may reflect a very slight degree of alkalosis due to exhalation of $\mathrm{CO}_{2}$ from the carbonate anion, but the reason for the delay after ingestion

Table 3. Urine Caicium Increments after Ingestion of Test Calcium Sources*

|  | 0-5 hours |  |  | 5-24 hours |  |  | 0-24 hours |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | N | Mean | SEM | N | Mean | SEM | N | Mean | SEM |
| Os-Cal | 23 | 21 | 3 | 22 | 22 | 8 | 22 | 43 | 10 |
| Ciracal | 23 | 16 | 3 | 22 | 30 | 10 | 22 | 45 | 9 |
| $\mathrm{CaCO}^{3}$ | 21 | 20 | 4 | 20 | 20 | 10 | 20 | 38 | 9 |

mg Ca nbove the cornesponding cxcretion following the blank load

Table 4. Cost: Benefit Analysis of Tro Calcium Supplements

|  | No. of tabs per boule | Men and woucd ayed $=05$ years$(\mathrm{n}=33,540 ; 000)$ |  |  |  | Women aged $\geq 75$ years$(\mathrm{a}=9,426,000)$ |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Cost per person 1 year (\$) <br> (I) | Cost for 1 year ( ${ }^{1}$ million) <br> (2) | $\begin{gathered} \text { Ner } \\ \text { benefit } \\ \text { ( } \$ \text { million) } \end{gathered}$ <br> (3) | Nes per-capits benefit (\$) (4) | Cost per person 2.83 year (\$) (5) | Cost for 2.93 year ( ( million) (6) | ```NEt benefit ($ million) (7)``` | Nei per-capita bearifit (\$) <br> (8) |
| Os-Cal $500 \mathrm{mg} \mathrm{Ca}+200 \mathrm{NJD}$ | 75 | 68.62 | 2,302 | 140 | 4.18 | 194.20 | 1,831 | -169 | -17.88 |
| Os-Cal $500 \mathrm{mg} \mathrm{Ca}+200 \mathrm{IJD}$ | 160 | 58.54 | 1,963 | 478 | 14.26 | 165.57 | 1,562 | 100 | 10.65 |
| Citracal 200 mg Ca | 200 | 86.69 | 2,907 | -466 | -13.89 | 245.34 | 2,313 | -651 | -69.02 |
| Citracal 200 mgg Ca | 100 | 116.25 | 3,399 | -1,457 | -43.45 | 329.01 | 3,101 | -1439 | -152.69 |
| Citacal $315 \mathrm{mg} \mathrm{Ca}+200 \mathrm{MUD}$ | 60 | 123.02 | 4,126 | $-1,684$ | -50.22 | 348.16 | 3,282 | -1620 | -171.84 |
| Citracal $315 \mathrm{mg} \mathrm{Ca}+200 \mathrm{IU}$ D | 120 | 92.02 | 3,086 | -645 | -19.22 | 260.44 | 2,455 | -793 | -84.12 |

on is the estimated 1995 prpulation sizo.
(1) Mass market costs (AC Nielsmen) for one year's supply for one person at $1,000 \mathrm{mg}$ elemental calcium per day.
(2) Cost for one year's supply far this population (N $\times(1)$.
(3) Preyenmble cotal expenditures ( $\$ 2,442$ million for 2995 in this population) minus the cost of surplying the entire popularion for one year ( 7 ),
(4) Nat beatitit divided by the population size ( $(3) \div \mathrm{N})$.
(5) Muss market cosis (AC Nielson) for 2.83 yeats' supply for one person is $1,000 \mathrm{mg}$ elemental calcium per diry.
(6) Cost fer 2.83 years' supply for this propulation (i) $\times$ (5)).
(7) Preventablo tolal expenditures ( $\$ 1,662$ million for 1995 in this population) minus the cost of supplying the encine population for 2.83 years ( 6 ).
(8) Wet benefit divided by the popilation ( 7 ) $\div$ N).

NB: Calculations based on Tubley VI, VII. From: Supplemental Calcium for the Prevention of Hip Fracnure; Rotential Health-Economic Benefits [4]. PapsikB_Cost Ca Supp (revised 3/5/01)
is unclear. Physiologically, these changes axe mutually consistent, since a higher ionized calcium would be expected to leail to a greater depression of PTH rclease, to an increased filtered calcium load at the kidney and, through lowered PTH, to decreased tubular reabsorption of calcium. Although the grealer rise in urine calcium with calciura cirate was not statistically significaut in this study, it is worth noting that Heller et al. [7] reported a significant loss of calcium in urine following supplementation with calcium citrate (Cirracal(1)) which was not seen with an equivalent dose of calcium carbonate (Os-Cal(D).

We bad not designed the study to evaluate this issue, and, indeed, we had not anticipated it. Nevertheless, it is worlb noting that the finding of a slight increase in calcium excretion with the citrate source is consistent with what we had teported previously [8]. In that earlier investigation, despite identic: tracer-based absorption fractions for the citrate and carbonate salts of calcium, there was a tendency for the urine calcium increment to be greater with the citrate than with the carbonate. We had auributed that finding to a calciuric effect of absorbed citrate, buy in view of the ionized calcium findings in this study, it may, instend, reflect a mild alkaloiic effect of the carbonate salt.

On a methodologic note, it may be worth mentioning that the increments in wrine calcium were substantially more variable than the increments in serum calcinm. The codfficients of variation (CVs) of the serum and urine calcinm increments at their peak values ( 3 and 5 hours for senum and 0 to 5 hours for urine), for all calcium sources, were $38 \%$ to $60 \%$ for serum and $77 \%$ to $99 \%$ for uripe. This roughly twofold greater variability underscores, as we have noted previously [8], the relative
weakness of using the rise in urine calcium to estimate absorptive performance, particularly for loads as small as 500 mg .

For this study, the retail cost per 1000 mg of ingested calcium was between $\$ 0.16$ and $\$ 0.20$ for the marketed calcium carbonate product and between $\$ 0.24$ and $\$ 0.38$ for the markered calcium citrate product Since both sources exhibited equivalent bioavailability, it is clear that the carbonate source Was the less expensive of the two per unit of absorbed calcium and would therefore exhibit a more $\hat{\text { favorable cost-benefit re- }}$ lationship in a cost-effectiveness analyses such as set forth in Table 4. Additionally, although not usually considered in cost bencfit analysis, the greater calcium density of carbonate-based


Fig. 4. Time course of serum ionized calcium expressed as a percent of rotal serum calcium for the three calcium sources. Error bars are I SEN (Copyright Robert P. Heaney, 2000. Used with permission.)
products means that fewer pills are needed to achieve a desired supplement intake, a factor known to influence padient compliance [15].

In this study we used $25(\mathrm{OH}) \mathrm{D}$ as a rapid and eflicient means of ensuring approximately equivalent vitamin $D$ status in all subjects. Such treatment would nat be a part of popula-cion-level supplementation, and its costs are, accordingly, not a part of our calculations. Vitamin $D$ is contained in botio of the supplements tested here, and its cost is, therefore, alfeady factored into the analysis summarized in Table 4.

While twe tested only two commercially available products in this analysis, our purpose was not so much to contrast these two specifically as to use them as examples for a type of calculation and analysis that should be performed for all marketed calcium supplement products. It was beyond the scope of this project to undertake an exhaustive survey of different pharmacentical formulations, although we believe this should be done. It is a matter of commonplace experience that there ire many other calcium products, available, at least some of which explicitly meet the USP disintegration and dissolution stimdards for calcium supplements (and therefore can be presumed to have a bioavailability comparable to what we found here). Their prices range from as low as $\$ 0.09$ per 1000 mg to as much as $\$ 0.53$. Lacking bioavailability data for most of these products, it is uncertain whether any of them would exhibit an advantage over the products tested here.

In conclușion, based upon bioavailability, cost and clinical efficacy, calcium carbonate, in the form of $\mathrm{Os}-\mathrm{CalB}$, would appear to be a good choice for çalcium supplementation in a US populacion at risk for both low bone mineral density arid hip fracture.

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[^2]:     adjusted means for Os-Cal and Citracal was expronendated for the rano. The upper and lower confirence boudis on the differeuce between the adjusted means were exponentinced for the spper and lower bounds on the rabio fresented in the table.

