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Supplemental Text

Letter from Dr. George Beaton to Dr. Scott Grundy
October 26, 1997

This letter was sent by Dr. Beaton to Dr. Grundy in response to several questions that Dr. Grundy had posed to Dr. Beaton. Dr. Grundy at the time was serving as a member of the Institute of Medicine's Standing Committee on the Scientific Evaluation of Dietary Reference Intakes.

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Dear Scott:

I'm not sure where it is best to begin. We agree on a number of basic points but I think you have left the conceptual framework rather radically in later points.

To settle where we agree, I remind you of an old, but very good adage "If it ain't broke, don't fix it!" The question that MUST be asked but, in my opinion has not, is whether there is any good evidence to indicate that raising existing calcium intakes would be expected to lower the age and gender-specific prevalence and severity of osteoporosis or its marker in populations, fracture rate. If there is no such evidence then the *a priori* assumption must be that the existing intakes (and their distribution) are satisfactory. That does not, in any way negate the role of supplementary calcium, along with appropriate medication, as a part of the treatment of osteoporosis. My question really addresses the perpetual epidemiologic issue – do we have evidence of a causal link and evidence that existing calcium intakes limit bone formation/achievement of peak bone mass and that peak bone mass relates causally to the age of onset of clinically significant osteoporosis. Walter Willett has expressed the very strong opinion that such evidence is lacking except perhaps for very low calcium intakes - i.e. he feels there is not epidemiologic support for raising the intakes and certainly not to the degree that would be implied by the arguments presented in the DRI report. [For your information, I filed a report with the Food and Nutrition Board advising that there were at least two fatal flaws in the argument presented in support of the particular numeric estimates. After sending my report out for expert review, and after a lot of discussions among themselves as well as a 1.5 hour conference call in which I was a participant, I THINK the Academy has accepted that the logic of the present calcium report is seriously flawed, and that the evidence and arguments must be reconsidered. Of course, I do not know what such reconsideration will lead to but I hope that the numbers end up being reasonable.]

Returning to your submission, the EAR is the average of the requirements of individuals. This is VERY different from the average intake of a population/group of individuals all of whom are well nourished. For energy, but not nutrients, the average requirement and the average intake of a well-nourished group are likely to be very similar. For energy, we think that on a chronic basis, there is a regulatory process, albeit not well understood, that keeps energy intake and energy expenditure in close balance, giving rise to an expected strong correlation between intake and requirement and a likely near-superimposition of the intake and requirement distributions. For nutrients, if we control for common denominators such as body sizes (e.g. for protein), energy intake (notably for thiamin), etc, and take care to define the criterion of requirement so that this is not allowed to slide in response to intake (a big issue in discussions of iron) there is no reason to believe that intakes and requirements are correlated. We must think of the two distributions as independent.

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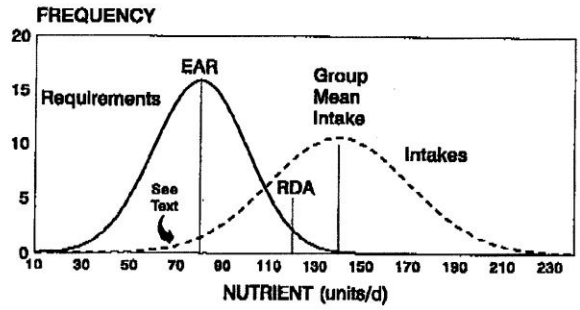
Where this takes us is the recognition that if EAR is meant to represent the average of individual requirements and the RDA is meant to be a point in the distribution of those requirements, those terms cannot be applied to the distribution of observed intakes. Adequacy/inadequacy/population risk of inadequacy/the expected prevalence of inadequate intakes must be thought of in terms of the interfacing of the two distributions (requirements and intakes). I have the temerity to try to represent this diagrammatically in the figure below. This figure simulates a hypothetical distribution of requirements with mean 80 and SD 20; it assumes, for simplicity, a normal distribution and sets the RDA as per existing convention at the mean + 2 SD. Only some 2.3% of individuals would be expected to have actual requirements greater than the RDA. The DRI report has accepted those same

INTAKES AND REQUIREMENTS
SIMULATED DISTRIBUTIONS



Intakes: Mean=80; SD=20

Requirements: Mean=140; SD=30

conventions but has applied the name Estimated Average Requirement (EAR) to designate the central point. The figure shows the position of the EAR and RDA on the requirement distribution. The requirement distribution is seen as generic applying to all 'populations" of individuals sharing the same characteristics recognized as affecting the requirement (usually gender, age, body size, etc. – the unidentified sources of variation contribute to the variability of requirement portrayed in the graph)

The figure also portrays an independent intake distribution., this time applying to a theoretical finite group/population of individuals. To achieve a "low population risk of inadequacy" we wish to position the intake distribution such that very few members of the group would have intakes below their own true but unknown requirement. In recent years, it has been demonstrated that the proportion of individuals with intakes below the average requirement (the EAR) provides a reasonable estimate of the expected prevalence of inadequate intakes. It does not identify the individuals with inadequate intakes, only the proportion. That is, in classical terms, there are major classification errors but the false positives and false negatives tend to cancel out under practical conditions. In turn, this gives us a way of deriving the "desirable" position of the group/population intake distribution. In the figure above, the intake distribution has been positioned such that 2.3% of the area under the curve falls below the EAR (see the arrow on the diagram). This results in a prediction that the prevalence of inadequate intakes in that population (or "population risk") would be about 2.3%. By the convention used in setting the RDA, this might be seen as an acceptable population risk. If not, one can shift the

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intakes to the right (upward) and reduce the area marked by the arrow, resulting is a reduced population risk.

In a nutshell, that is the current state of conceptual frameworks embodied in the DRI report, but the terminology has not caught up. One term we need would relate to the Estimated Necessary Group Mean Intake as portrayed in the figure above. Note that this number can be derived from a knowledge of the EAR and an estimate of the shape of the intake distribution (normality is a convenient assumption but absolutely not necessary condition as I will illustrate later).

Now, in your diagrams, you seem to assume that the Mean intake and EAR are identical. In the existing conceptual framework, that would be true only for Energy.

You also assume, very explicitly, that the task of the DRI committees is to estimate the required group mean intake. That is nether neither their mandate nor their perceived goal. They are trying to estimate the EAR as described in the figure above. Estimation of the necessary group mean intake is seen as an application and a still-to-be-funded committee is supposed to address that. I will now offer you a perhaps bewildering ,but unfortunately all too realistic, illustration of the application of these principles and approaches to a situation now very close to home. Below is a figure I will be using in a talk on October 30.

The figure first portrays the observed distribution of intakes of calcium by women 31-50 years of age living in the United States. These are the most recent USDA 1994 CSFI data adjusted to eliminate the effect of day-to-day variation in intake (using the Iowa State University methodology). It is an estimated distribution of "usual intakes". I emphasize that it is real not hypothetical.

On that distribution is shown a still-hypothetical EAR of 700 mg/d (about half of the AI originally suggested as an EAR by the calcium panel and finally called an AI following serious arguments about what had actually been estimated. I chose 700 for this illustration because I personally doubt that the true EAR for this age group can be more than that and also because if a higher EAR is chosen the portrayal becomes too absurd to imagine – not because the portrayal is wrong but because the implications of what it says become totally unacceptable in our experience. We simply have no experience with intakes as high as would be implied and that, to me, is truly frightening – that a body like the National Academy of Sciences could go on record seemingly advocating, for the U.S. (and Canadian) population a shift of intakes into a region where we have no experience concerning either benefit or harm. I see it as highly dangerous.

What the figure then attempts to show is where the intake distribution would have to be positioned (average intake = Necessary Group Mean Intake) to achieve a population risk of about 3% (3% of individuals below the EAR). I portray two models for shifting the distribution. The first simply moves the distribution up by about 440 mg . This might only be seen in reality if everyone took a calcium supplement providing exactly 440 mg/d. I think of this as a minimalist conservatism. In the other approach, suggested to me by Alicia Carriquiry at Iowa State University, intakes have been increased proportionately for everyone. That is, each person shows the same % increase but big intakes increase more in absolute amount that do low initial intakes. That sort of situation could well occur with uncontrolled fortification (which is why I used it) and perhaps also if everyone accepted the sort of dietary advice "eat more good sources of calcium" Anyway, I see this as a sort of quasi-maximal situation (I can certainly portray worse scenarios but this is bad enough). I think that in reality the actual picture that would emerge from an attempt to implement the sort of advice likely to emerge from the DRI calcium report will fall between these two [if the EAR is as low as 700 - if it is 1000 or more, which I fear they will suggest, then the intake distributions shift sharply to the right and the problems become overwhelming.

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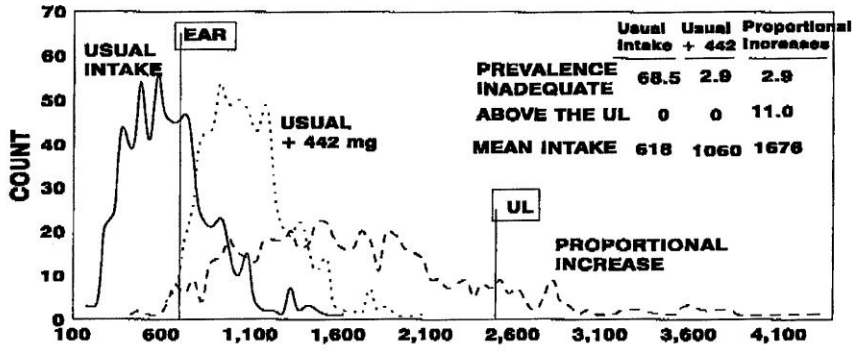
IMPACT OF TRYING TO MEET AN EAR = 700 mg/d
U.S. ADULT WOMEN 31-50 yrs
A. IMPACT ON CALCIUM INTAKES



Data from USDA 1994 CSFI adjusted with SIDE to estimate the distribution of usual intakes.

N = 590 Subjects

As the figures in the upper right hand indicate, the initially estimated prevalence of inadequacy among the 590 women would be estimated as about 70%. By shifting the intake distribution upward, the estimated prevalence of inadequate intakes falls to about 3% but, with the proportional increase model, the proportion of intakes falling above the upper limit (to avoid risk of Milk Alkali Syndrome) is more than 10%.

The DRI report, does not consider the impact of calcium on iron availability to be sufficiently important to warrant attention is setting safe upper limits to intake. The still-unpublished Canadian report on risk assessment does direct attention to iron and, without attempting to explain or justify how the calculations were done, MY interpretation of the Canadian synthesis of iron impact would lead to the possible portrayal shown overleaf. Here the available iron figures are reduced in accord with the Canadian model using calcium intakes (and concurrently estimated iron intakes for the distributions shown above). The requirement figures are taken from the FAO/WHO, 1988 report on iron requirements. Assessment was done using the probability approach described in a 1986 FNB report on assessment of observed intakes. The results of this exercise are portrayed overleaf.

The FAO/WHO committee followed the advice of the 1986 FNB report and attempted to define requirements for different criteria of iron status. In iron this is particularly important since the utilization ("bioavailability") of dietary iron changes very significantly with iron status. Further, for planning (and hence assessment) purposes, not all would agree that it is necessary to achieve and maintain substantial stores of iron in most women (the criterion implied under "maintain stores"). Indeed, because the RDA based on such a criterion seemed unlikely of achievement with anything but supplementation or extraordinary dietary practices, the FAO/WHO committee did not even list the numeric estimates that would be associated with this criterion of adequacy. They did present the basis of the calculations and that is what I have used in the illustration. For the actual measures that would characterize these three criteria of requirement, see the original FAO/WHO report. The "normative" requirement prevalence estimates are presented here because many in North America argue that

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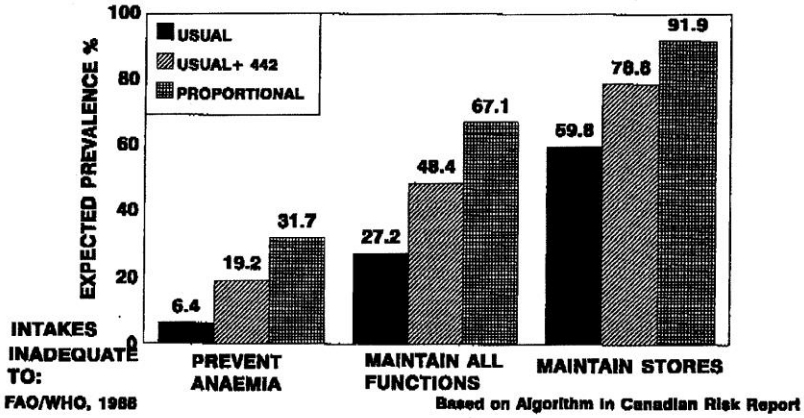
substantial stores are important and should be achieved. I think you will immediately see the potential impact high calcium recommendations will have when an iron sub-committee is eventually convened and starts debating the levels of iron that must be recommended for "optimal health", given preexisting recommendations for very high calcium intakes.

POSSIBLE IMPACT OF TRYING TO MEET AN EAR = 700 mg/d
US ADULT WOMEN 31-50 yrs
B. IMPACT ON IRON UTILIZATION

ILLUSTRATIVE EXAMPLE OF TREND. VALUES UNCERTAIN.



My point is simple, but the solution is complex. If indeed the DRI process is intended to establish "requirements" for optimal nutrition, then it cannot proceed by the conventional approach, looking at one nutrient at a time. We know for example, that the etiology of osteoporosis (and cardiovascular disease, cancer and the rest) is multifactorial. It seems very likely that the influencing factors are interactive, one conditioning another; they cannot be considered in isolation. The example I offer of calcium and iron is but another example of a different type interactions we know exist.

I truly believe that the DRI process, as now envisaged, has impossible goals. The process and the conceptual structure of numbers and names are not the main problem – it is the conception that one can estimate the specific, context-independent contribution of individual nutrients toward this nebulous goal of "optimal health and nutrition". I think we can develop general dietary (food selection) guidelines for use in pubic education, but I don't think we have nearly enough knowledge to translate the information supporting these guidelines into specific nutrient requirement estimates and I fear we are going to create serious problems if we try to make such estimates and then base government policy on those numbers.

Let me return again to the terminology issues you raise. If we cannot estimate an EAR by conventional evidence, and particularly not using the conventional weight that experimental scientists place on well-controlled small group and finite time depletion-repletion or balance studies, then I think the only path open is either a matter of informed judgement (the Consensus Conference approach) or an approach that places very heavy reliance on epidemiology and then looks to the

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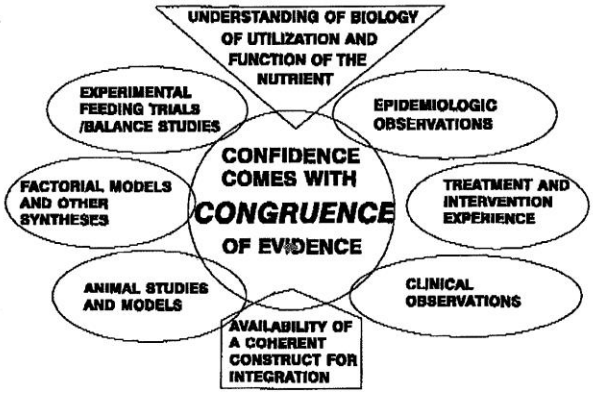
detailed metabolic/experimental sciences to try to interpret/refine the interpretation of the epidemiologic data. That is certainly not what has been done for calcium so far but I think that that approach is likely what was intended when the term AI was coined and defined in the DRI series. It is described as an estimated of the average group mean that is consistent with the maintenance of good health in almost all members of the population. Conceptually the AI is the average of the intake distribution portrayed in my first figure but having risk of outcome A (e.g. osteoporosis) instead of a requirement distribution. That is not what the calcium group tried to estimate; applying the term AI to the result of their deliberation was an unfortunate and confusing (for the rest of the report) action. Of course, if the data are good enough, then one can begin to move backward from the population intake and its distribution to derive an estimate of the likely EAR. As suggested in the first figure, the group mean intake will have to be much higher than the EAR. [and in situations where the concern is excess intake rather than inadequate, some of the directions will change – for example, the group mean intake would have to be sufficiently low to minimize the risk of "toxic"/deleterious effects]. With adequate data the AI as conceptualized here (coming only from the identification of populations or sub-populations where intake is adequate to prevent the undesirable outcome) and the "necessary group mean intake" derived from a base of information about requirements and intake distributions would be the same. Distinction in terminology would be intended to reflect the approach to derivation and perhaps confidence in the derived figure, not to distinguish conceptual meaning or application.



Finally, Dr. Grundy, I argue, very strongly, that where we are all falling far short of the mark and failing our real obligations as scientists in that we are wearing blinders and not really attempting to do what must be done – synthesize and integrate different lines of evidence. Above is a figure I have used in a few meetings in the last couple of years. I feel we (particularly the experimental scientists) don't take the message seriously.

Sincerely

George H. Beaton
Professor Emeritus

P.S. I will mail you this letter in hard copy along with a preprint of a chapter now in press for the next edition of Modern Nutrition in Health and Disease. I think you will find it interesting and germane.