This is Dr. Heaney's final blog post

One of the more courteous features of Western civilization is the respect it commonly affords deathbed statements. They may be wild and wacky, sometimes even profound, but they're seldom dismissed out of hand. Presuming on that courtesy, I take this one last chance to offer some observations that I've long pondered and that touch deeply the church that I love – the church that Hans Kung many years ago called *Ecclesia semper reformanda*. Of many issues, Three unrelated matters come to mind: i) the gift of Protestantism; ii) the misunderstanding and abuse of the second commandment; iii) the ordination of women and with it, the constricted sense of congregationalism within Roman Catholicism

The Gift of Protestantism: Historians recognize three "hinge points" in the history of Christianity: the so-called Council of Jerusalem, the edict of Constantine, and the Protestant Reformation. Each profoundly changed the church and shaped it as we know it today.

This last is my concern here. A prominent Protestant theologian commented a few years ago that Protestantism had run its course and that it had done its work. What had that work been? What had it given to the larger Christian Church? Three gifts stand out: the vernacular, the Bible, and congregational sensitivity. Today we are able to worship and read the scriptures in our native tongues. Otherwise they'd be a closed book. What a gift! That's new since the Reformation. Amazingly, the bible itself had been effectively off limits for Roman Catholics up till just about 70 years ago. German Lutheran theologians reversed that in the 19th century. Since then there's been a tremendous flowering of Catholic scripture scholarship in both Europe and North America, of which we are all beneficiaries.

Congregationalism: The Roman Catholic corporate model has been characterized (wrongly) as having a CEO in Rome with "branch offices" around the world, and with orders coming down the chain of command. A tremendous emphasis has been placed on uniformity of both doctrine and practice. That was not how the early church functioned and it is not how Pope Francis seems to see things. Protestantism typically affords more autonomy to individual congregations and communities. Pope Francis, it seems, believes that a decision reached in North Africa may not be fully appropriate for North Omaha – a conclusion the Early Fathers would likely have agreed with. From the very beginning, Christianity has always been a "community of communities." In this way, Protestantism has preserved for the Christian Church not just the Bible, but some of its own heritage as well.

Without the Reformation, we might have had none of these. So, thank you, Martin Luther.

The Second Commandment: For many Christians, and certainly for Catholics, the second commandment is mostly about revering the Holy Name and avoiding cursing and salting our language with "Jesus Christs!" and similar imprecations. But that can't have been what God was pointing to when Moses got the law on Mt. Sinai. The Hebrews weren't, so far as we know, cursing and swearing the way so many do today in ostensibly Christian cultures. No, they invoked God's name to emphasize and put God's authority behind what they themselves were thinking and saying – in other words to put into God's mouth their own decisions and conclusions. In Mark's Gospel (Mk 7:9) Jesus tells the Jewish establishment: "How ingeniously you get around the commandments of God in order to observe your own tradition!" Such seems to be the besetting sin of all hierarchs then and now.

I remember reading, in John O'Malley's "The History of Vatican II," his statement that at the time of the great East-West schism the heads of the two branches of Christianity each

solemnly excommunicated one another's entire Christian populations. I literally couldn't decide whether to cry or laugh Actually, I did both. The thought that God was waiting in the wings to exclude from Heaven nearly half the human race simply on the say of pope or patriarch was so patently absurd as to be both blasphemous and hubristic – downright comical, actually. Clearly we need to exercise some economy of our pretensions! The authority of the teaching office has to be based in reality, not in hubris.

The ordination of women to the clerical state: The ordination of women is something Catholics are not supposed to talk about – or even think about. But how can you not think about the 800 pound gorilla in the room? There is, I think, one compelling reason why we must find a way to meet this challenge – find a way to ordain women and gain acceptance of the decision among the body of the faithful. The arguments for or against doing so from Scripture, theology, biology, women's rights, staffing needs, or what Jesus did (or didn't do) do not seem to me persuasive. The solution lies, I think, in the last of the gifts from Protestantism. We should ordain women because the Christian community needs them in that role. It's just that simple.

What is good for (promotes the "health" of) the community/congregation has to be the criterion of the rightness of what we do. Our highly individualistic, atomized approach to such decisions marginalizes (basically, ignores) the needs of the congregation. We *need* the special charism of women priests. (For that matter we need the special charism of male priests, as well.) The community/congregation *needs* both. That basically is why we must have both.

Posted in Uncategorized | Tagged Catholic, church, Protestantism | Leave a comment

VITAMIN D AND THE HUMAN FAMILY TREE

Posted on August 11, 2015 by Cindy Workman
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Why the Neanderthals Lost the Race

Based on both physical and DNA evidence, anthropologists classify humans as members of the family of great apes, which includes orangutans, gorillas, and chimpanzees, as well as various human species. The branch to which we modern humans belong includes at least six species belonging to the genus Homo whose fossil remains have been found in East Africa over the past 60+ years. There was once a tendency to think of the latter as ancestors of modern humans, as if they were stages up a single branch of the tree, rising from primitive to advanced over hundreds of thousands of years, with Homo sapiens at the very tip, i.e., the "highest" form of human. On the contrary, the human family tree is both more complicated and more interesting. These various other members of the genus Homo are now recognized as separate twigs off the human branch of the great ape lineage. They are not so much our ancestors as our cousins. That branching continued to occur for millennia alongside the twig that we now recognize as modern humans (Homo sapiens). Some of those other humans made it to Europe before we (Homo sapiens) did.

The migratory path of the several human groups took them north out of Africa, then through the Middle East, ultimately colonizing Europe and Western and Southern Asia. Evidence for

the European in-migration of Homo sapiens is clear and points to a time about 40,000 to 50,000 years before the present. But that's not early enough to qualify as "first." The discovery of settlements by other species of Homo throughout Europe, extending as far east as Western Siberia (e.g., the Denisovan people, >50,000 yrs ago), indicates that they predated the arrival of Homo sapiens by thousands of years.

The best studied of these earlier migrants out of Africa are the Neanderthals, whose remains and cultural artifacts are found throughout Europe, and who clearly precede the arrival of Homo sapiens. Anthropologists and paleontologists have puzzled over how it was that Homo sapiens, as late arrivers, came to displace the Neanderthals. Many theories have been proposed, ranging from superior weapons and technology to superior intelligence, and most recently to the use of what Scientific American termed "the ultimate weapon," cooperation.

For the most part, these explanations have not been completely satisfying. Nevertheless, one factor does seem certain: Homo sapiens effectively "swamped" the Neanderthals. There were simply many more of us than of them. But that alone does not explain the apparent, complete disappearance of the Neanderthals. DNA evidence indicates that there was some limited interbreeding between resident Neanderthals and immigrant Homo sapiens. So, in one sense, some of the Neanderthal genome has survived. Interestingly, the presence of Neanderthal DNA in the modern human genome, which amounts to something like 2–3 % of the total genome, is largely confined to modern Europeans and Asians, indicating that the interbreeding occurred after the arrival of Homo sp. in the Middle East and/or Europe.

Still, why did the Neanderthals disappear from Europe? Recently, Leonard Greenfield, a physical anthropologist/paleontologist at Temple University, has set forth a persuasive case for a critical role of vitamin D, both in shaping the evolution of modern humans, and in explaining the disappearance of the Neanderthals.
It is generally agreed that the ancestral home of all of the various Homo species was East Africa, a location that would have provided abundant vitamin D in the form of sunlight. (Solar UV-B radiation converts a precursor compound into vitamin D.) Contemporary individuals from East African tribes exhibit a vitamin D status, derived mainly from cutaneous synthesis, which is equivalent to what would be produced in a Caucasian by a purely oral intake of 5,000 to 8,000 IU/day. However, it is also known that solar input of vitamin D inexorably diminishes as individuals move north out of equatorial latitudes.Thus north-migrating peoples coming out of East Africa pretty much all faced some degree of vitamin D deficiency.

That fact is generally considered to be the main explanation for the rapid loss of skin pigmentation among the migrating tribes of Homo sp. The heritable mutation that lead to the shift to pale skin thereby enhanced cutaneous synthesis of vitamin D and thus partially offset the diminished solar UV-B irradiance at higher latitudes. Individuals without that change in skin pigmentation would have been even more seriously vitamin D deficient than the others, and their pelvic bone structures could have been so distorted by D-deficiency rickets that delivery of babies from below would have been difficult or outright impossible, leading ultimately to extinction of those tribes and families that failed to develop pale skin.

But that simply means that all migrants coming out of Africa would have had marginal to deficient vitamin D status. The farther the northward migrants got from their place of origin, the worse their vitamin D status. But that tells us nothing about why Neanderthals, particularly, lost the race to survive in Europe. The only sources of vitamin D available to European Homo sp. would have been what little sun exposure might have been available and a diet rich in seafood & marine mammals. The high latitude of most of Europe and its

extensive and persistent cloud cover mean that most individuals would have gotten little vitamin D by the solar route, which leaves only food. Greenfield points out that only the Homo sapiens immigrants had developed cultural practices that included fishing and/or eating the meat and fat of marine mammals. As a result, the Homo sapiens "immigrants" would have had been better able to achieve and maintain a healthy vitamin D status than the Neanderthal "natives".
But general health, alone, is probably not a satisfactory explanation for what appears to have been the fairly rapid extinction of the Neanderthals. There's more to the story. Adequate vitamin D status is absolutely essential for an organism to mount an adequate immune response, particularly in the face of foreign antigens, to which the "natives" would have had no prior exposure. (There are many contemporary examples of populations being "wiped out" by infectious diseases with which they had had no experience, brought to them, even if unwittingly, by "discoverers" or colonizers.)

Thus it appears likely that native, Neanderthal populations, would have declined both in numbers and in dominance simply because, unprotected by adequate vitamin D and hence with compromised immune competence, they succumbed to diseases brought to them by the invading Homo sapiens, whose vitamin D status was better and who, in addition, had inherited some degree of resistance to the diseases concerned. Also, as just noted, the invaders had dietary practices that, in comparison to Neanderthals, better suited them to live and thrive in a vitamin D-deprived environment (i.e., fish eating). Presumably, had the resident Neanderthals been able to achieve a more adequate vitamin D status they would have been better equipped to deal with the diseases brought to them by the invading Homo sapiens migrant bands.

There is a moral to this story, namely that nutrition is important after all, not just for the health of individuals, but for the survival of whole populations. But there is yet another insight to be gained. We are able to discern the association between poor population-level survival and low vitamin D status in the Neanderthals, but only from our great distance in time. Individual Neanderthals with inadequate immune competence would have been prone to become sick or to die, but up close one could not have been certain that it was the vitamin D status that was responsible, even if we had been there. Nor would every individual with low vitamin D status have succumbed. There is great deal of variability in sensitivity to, and need for, vitamin D from person to person. It's just that, considering the population as a whole, the risk of a Neanderthal individual's developing one of those unfamiliar diseases would be elevated, and, as a group, Neanderthals would thus be less competitive in a Darwinian sense. This was the reason Greenfield puts forth and it seems the most satisfactory of extant explanations for the fact that the Homo sapiens population grew and prospered, while the Neanderthal population, already fewer in numbers, shrank.

Further reading:
Greenfield, L.O. Vitamin D Deficiency in Modern Humans and Neanderthals. (2015). OutskirtsPress, Denver, CO

Posted in Nutrient intake requirements, Nutrition, Vitamin D | Tagged DNA, homo sapiens, nutritional deficiency, sunlight, vitamin D | Leave a comment

The IOM Miscalculated Its RDA For Vitamin D

Posted on February 13, 2015 by Robert P. Heaney
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Last year (2014) saw an unusual event. Two statisticians at the University of Alberta in Ednonton, Canada (Paul Veugelers and JP Ekwaru) published a paper in the online journal Nutrients (6(10):4472-5) showing that the Institute of Medicine (IOM) had made a serious calculation error in its recommended dietary allowance (RDA) for vitamin D. Immediately, other statisticians checked the Canadians' analyses and found that, indeed, they were right. Together with my colleagues at Grassroots Health, I went back to square one, starting with a different population entirely, and came to exactly the same conclusion. The true RDA for vitamin D was about 10 times higher than the IOM had said. Not a small error. To understand, how this might have happened and why this is important, some background may be helpful.

Background
An RDA is technically the amount of a nutrient every member of a population should ingest to ensure that 97.5% of its members would meet a specified criterion of nutritional adequacy. For vitamin D, the IOM panel determined that the criterion for adequacy was a serum concentration of a particular vitamin D derivative (25-hydroxyvitamin D) of 20 ng/mL or higher, and that for adults up to age 70, 600 IU of vitamin D per day was the RDA.

Both of those figures provoked immediate and unprecedented dissent from a diverse group of nutritional scientists, but the disagreement centered mostly around the IOM panel's reading and interpretation of the evidence, rather than its calculation of the RDA. The Edmonton statisticians took the dissent a step further, showing that the actual calculation was itself wrong. Here's what seems to have happened.

What Happened
Not everyone gets the same response to a given intake of any particular nutrient, i.e., some require more than others to reach the specified target, and while the average response to a certain dose of vitamin D may be above the target level, a substantial fraction of a population can still be below it. Thus, the RDA will always be higher than the average requirement, and for some nutrients, substantially so. As a consequence, ensuring that every member of a population receives the RDA guarantees that 97.5% of that population will be getting at least enough, while many will be getting more than they actually need.

The IOM panel identified a number of published studies showing the 25-hydroxyvitamin D response to various vitamin D doses. They plotted the average response in each of those studies against dose, thereby generating what is termed a "dose response curve", i.e., a way to estimate how much of a response would be predicted for any given vitamin D intake. But, to make a long story short, because it used average responses, that curve tells us nothing about the intake requirement for the individual members of a population, and particularly those whose response to a given dose falls in the bottom 2.5 percentiles. The IOM panel surely knew that the average intake required to meet or exceed 20 ng/mL was not the same as the RDA, as it would be inadequate for all those with below average responses (about half the population). So, to catch the "weak" responders, they calculated the 95% probability range around their dose response curve, designating as the RDA the point where the bottom end of

that probability range exceeded 20 ng/mL. While this might seem to have been the right approach, it was not. The panel appears to have overlooked the fact that the 95% probability range for their curve is for the average values that would be expected from similar studies at any particular dose. The dispersion of averages of several studies is, as every beginning student of statistics knows, much more narrow than dispersion of individual values within a study around its own average. And it's the 2.5th percentile individual values from those studies, not the study averages, that should have been used to create the relevant dose response curve.

It's this latter approach that the Canadian statisticians used. They took precisely the same studies as the IOM had used and demonstrated that the requirement to ensure that 97.5% of the population would have a value of at least 20 ng/mL, was 8,895 IU per day. Recall that the IOM figure was less than 1/10 that, i.e. 600 IU per day up to age 70 (and 800 IU per day thereafter). When my colleagues and I analyzed the large GrassrootsHealth dataset, we calculated a value closer to 7,000 IU per day, still a full order of magnitude higher than the estimate of the IOM, and not substantially different from the estimate of Veugelers and Ekwaru.

Why This Is A Problem

This is an important mistake, not simply because it shouldn't have been allowed in a major policy document, but because IOM recommendations have important effects on a wide array of government programs. These include nutritional standards for US military, for school lunch programs, for WIC and many others, both in the United States and in Canada.

Canada, which paid one third the cost of generating the IOM report, is in a particularly difficult situation. Its First Nations peoples, living near the Arctic Circle, do not get any vitamin D from the sun, as do those of us living at more temperate latitudes. They are totally dependent upon food and supplement sources. Their ancestral diets, based largely on seals and whales, constituted a rich source of vitamin D. They are much less commonly consumed today, in part because of the ready availability of low nutrient density foods flown in from the south, and in part because environmental pollution has made seal and whale products a source of dangerous toxins (as well as necessary nutrients). The Canadian government, responsible for the health of all of its citizens, can turn only to the existing IOM recommendation (600 IU per day) to set standards for the people living in its northern territories. But, as the Edmonton statisticians noted, that number is woefully inadequate.

There is almost no public awareness of this error or its implications in the United States, but that is not true for Canada. A large nutritional health foundation located in Calgary (Pure North S'Energy Foundation) has taken out a series of half page advertisements in Canada's national newspaper (*Globe and Mail*), alerting Canadians to the fact that the error was made and that they need more vitamin D than current policy indicates (http://www.purenorth.ca/?page_id=1356). The IOM, Health Canada, and the Canadian Ministry of Health have all been formally alerted to this problem. The Health Ministry has agreed to undertake an independent reanalysis of the calculation of the RDA, but the results are not yet available and the shape of the ministry's action is still uncertain.

How It May Have Happened

It's one thing to know how the mistake was made, and quite another to know how it could have happened. Here, one can only speculate, as the IOM processes are shrouded in secrecy. The IOM report was a massive document and it is likely that much of the background work, such as the literature search, the drafting of the report, and the statistical calculations, were

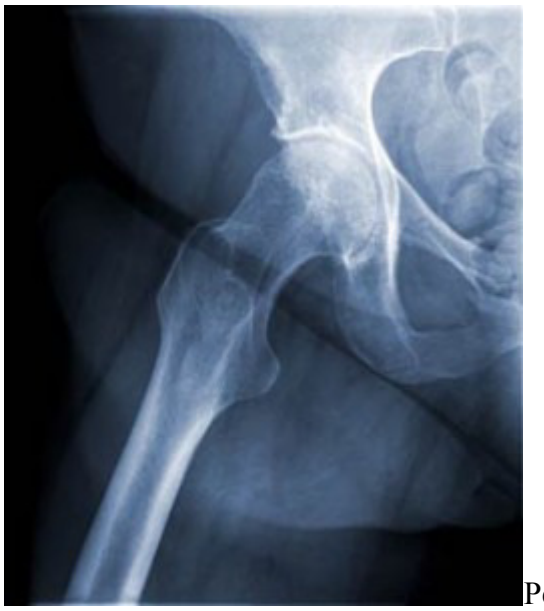
done by IOM staff members who may not, themselves, have been sufficiently expert in the vitamin D field to recognize discrepancies that might have popped up. (It is noteworthy that several of the dissenting letters submitted to scientific publications following release of the IOM report had specifically cited the fact that 600 IU per day was not sufficient to guarantee a level of 20 ng/mL.) It would then have been up to the expert panel to review and adjust this staff work. To be fair to the panel, it is important to understand that the scientific members of IOM panels are not compensated for their time and effort. They do it as a public service, and they are all busy scientists with work of their own. Still, it was their job, and one must wonder how they failed to see an error that was apparent to other equally knowledgeable, but outside, scientists.

Comment

There may be a moral here. It is widely recognized that many of the panel members, before coming together to review the evidence, had already staked out a position to the effect that, while the previous (1997) recommendation for vitamin D (200 IU per day) was probably inadequate, the actual RDA was almost certainly below 1000 IU per day. Accordingly, when the statistical calculations produced a number that matched their own expectations, they may not have been inclined to question its derivation.

There is a generally held belief that science is objective, data-driven. And to a substantial extent that is so. But science and scientists are not identical. Scientists often have strongly held opinions and, like people in general, find ways to construe the evidence to support their beliefs. When those beliefs are wrong, science, as a field, ultimately abandons them. I am confident that this IOM error will be corrected sooner or later. This is partly because it is demonstrably erroneous, and partly because the related set of IOM recommendations for vitamin D has not elicited a consensus in the field of vitamin D research. If the Dietary Reference Intakes produced by the IOM are important, then it is important that they be right. I can only hope that not too much human damage will occur as we wait for the needed correction to happen.

Over 30 years ago I gave a paper at an osteoporosis meeting in Jerusalem titled “The Paradox of Irreversibility of Age-Related Bone Loss.” By ”irreversibility” I meant that once the bone was lost there was not much that could be done to restore it.

 Perhaps “puzzle” would have been a better word than “paradox.” From our experience with other similar situations, we would have expected that the lost bone would be restored. The underlying facts are that during the postmenopausal period bone loss occurs rapidly as estrogen levels drop to low values. Estrogen replacement therapy started at menopause prevents that loss, showing clearly that it is the estrogen deficiency that is responsible. Similarly, severe calcium deficiency also leads to bone loss, and maintaining a high calcium intake does slow that loss, and perhaps even prevent it. And, as is generally recognized, low calcium intake and low estrogen status are common in contemporary women during the post-menopausal years. These factors are the principal reasons for age-related bone loss in women.

But neither estrogen, nor calcium, nor the combination of the two, will restore the lost bone after it is gone. This seemed puzzling because with many other nutritional and hormonal deficiencies, restoring the lost hormone or nutrient does generally return the body to its pre-deficiency state. Examples would be hypothyroidism, which responds to thyroid hormone replacement, and iron-deficiency anemia, which responds fully to replacement of the lost iron.

The explanations for this seeming irreversibility which I offered at the time were twofold. 1) bone building (or rebuilding) requires weight-bearing or impact exercise, and physical activity generally declines after midlife; so a condition necessary for rebuilding was missing. 2) much of the lost bone is trabecular in character, i.e., the spongy latticework in the center of bones such as the vertebral bodies of the spine; once that lattice is lost, there is no longer a scaffolding or framework on which to rebuild.

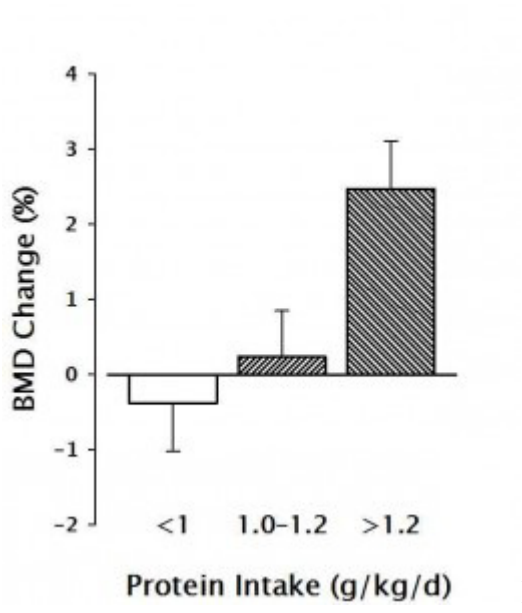
I believe that both reasons are at least partially correct, but today they seem to me far from satisfactory explanations for this puzzling irreversibility. There is, I think, a better, more complete explanation, one that can be tested (and thus proved or disproved), and one that, if correct, could revolutionize the treatment and prevention of osteoporosis.

Bone is not just calcium. It is made up, first of all, of a protein matrix within which the calcium salts are embedded. Soak a bone in acid and you remove the calcium. But what’s left still looks like the bone you started with, except now it’s rubbery rather than hard. It’s now all protein and no mineral. The key point is that, while bone is the body’s reservoir of calcium, that calcium is tied up as part of a structure, the largest component of which is protein. When the body needs calcium and has to make withdrawals from the skeletal reserves, it does so not by leaching the calcium from this protein-mineral complex, but by

physically tearing down microscopic units of bone and scavenging the calcium that is released in the process. Inevitably, therefore, the protein matrix – the structure – goes as well.

In order to profit fully from a high calcium intake, a patient who has lost bone needs to consume enough protein to allow the body to rebuild the lost structure. Otherwise all that a high calcium intake can do is to prevent the body's further tearing down of bone to meet the calcium needs of other body systems and tissues. That's a good thing to do, but it is not enough. Nevertheless, it is precisely to prevent that draining of the body's calcium reserves that a high calcium intake (whether from food or supplements) is today a vital part of the standard of care for patients with osteoporosis. Even so, the failure of nutritional replacement to rebuild lost bone is what originally set the stage for the entry of pharmaceutical agents, some of which can produce substantial bone rebuilding.

That landscape began to change a few years ago when an insightful investigator at the Tufts Nutrition Research Center on Aging in Boston noticed that a high calcium intake did, in fact, lead to increased bone gain if the patient's intake of protein was high. Bess Dawson-Hughes had previously published the results of a calcium and vitamin D supplementation trial, producing a better than 50 percent reduction in fracture risk in healthy elderly Bostonians with those two nutrients alone. But, like others before her, she noted that, while high calcium intakes reduced or stopped bone loss in her treated subjects, the two nutrients didn't lead to bone gain. They didn't, that is, in individuals consuming usual protein intakes. However, in a subset of her treated patients, who, it turns out, had protein intakes above 1.5 times the RDA (0.8 g/kg body weight), bone gain was dramatic (while it was zero in those with more usual – and usually thought "adequate" – protein intakes). The figure below shows the 3-year change in bone mineral density (BMD) at the hip in the calcium- and vitamin-supplemented participants in the Tufts study. Only with the highest protein intakes was there appreciable bone gain.



For me, it was an "Aha!" moment. Why hadn't we thought of that? It was known that bone is 50 percent protein by volume (but only about 20 percent calcium by weight). And it was known that when bone is torn down (as with estrogen or calcium deficiency), its protein is degraded in the process. So it made sense that, to rebuild the lost bone, you would need not just calcium but fresh protein as well.

When I first heard of this result, I immediately went to our own Creighton database on calcium metabolism in midlife women (the "Omaha Nuns Project) and looked to see whether

protein intake (which we had recorded and measured) made a difference in the bone metabolism of our nuns. There it was, just as the Tufts investigator had shown. Our nuns with protein intakes below the median for the group could not retain calcium, no matter what the intake (i. e., they couldn't build bone). By contrast, those with protein intakes above the median for the group retained extra calcium reasonably well.

So, here were two distinct data sets, two quite different investigations, exhibiting the same interdependence of calcium and protein. What we, and probably most clinical nutritionists, had failed to recognize, was that the adult RDA for protein is just barely enough to prevent muscle loss, and is not enough to support tissue building or rebuilding. But, as already noted, when calcium deficiency leads to bone loss, the bone protein is lost as well, and that has to be rebuilt to restore the lost bone.

This mutual dependence of calcium and protein provides a good illustration of two key (and often underappreciated) aspects of nutrition. The first is that nutrients almost always act together with other nutrients. The second feature is what Bruce Ames of the University of California, Berkeley, has called a "triage" system within nutrition. The body operates a triage mechanism, ensuring that the most vital functions receive the nutrients first and leaving the other tissues and systems of the body to get by on what is left over. It seems that this triage mechanism is at work with respect to adult bone rebuilding. With limited protein intake, the body ensures that its most vital functions are served first. Bone, in effect, gets the leftovers. We need a high protein intake precisely to ensure that there will be something left for bone.

Two unplanned observations such as those of Dawson-Hughes and our own Creighton group, even if they make perfect sense, would not generally be considered enough to change public policy, particularly when it comes to nutrient intake recommendations. So, if we are to be certain that supplementing *both* protein and calcium will permit rebuilding of lost bone, it will be necessary to mount one or more clinical trials testing that hypothesis.

Such a trial would likely be designed to start with a group of probably several hundred postmenopausal women who had already lost bone and whose protein intakes were in the range of the current RDA, that is about 0.8 g/kg/day. All would be supplemented with sufficient calcium to permit maximum bone building if the individuals concerned could, in fact, use the calcium efficiently. They would all also receive sufficient vitamin D to ensure a serum concentration of 25(OH)D of 40 ng/mL or higher. Then half would be given a diet, probably involving a protein supplement, which would raise their protein intakes to above 1.2 g/kg/day. [Some might argue that there should be a third group, one with protein intakes at the RDA, but without the substantial calcium and vitamin D supplementation envisioned above.] In either case, trial duration would be about three to four years, and the endpoint would be the observed change in BMD over that treatment period. The predicted outcome would be that the lower protein group receiving calcium and vitamin D would have no appreciable change in BMD, while the higher protein group, also receiving extra calcium and vitamin D, would exhibit clinically significant bone gain. As outlined here, such a trial could not be blinded, mainly because the diets would be perceptibly different.

Even if such a trial were to start today, it would probably be at least five years before the results would be clear and actions could be taken to change official recommendations and influence individual dietary behaviors. What should one do in the meanwhile?

This is a matter for individual decision, but it is helpful to know that high protein intakes are safe. Their principal negative impact is on the wallet, not the body (as rich protein foods tend to cost somewhat more than foods high in added sugars, for example, or other types of empty calories). For me the decision is easy; I'd opt for the high protein intake without a second thought (with, of course, adequate calcium and vitamin D, as well). As a dividend, I should note that there is one food group that is both a very rich source of protein and at the same time the principal source of calcium in the diets of first world populations – dairy. Moreover, if consumed as milk, its cost is less than the average cost of the other foods in your grocery cart.

Even if the trial were to be successful, It would be naïve to think that would be the end of the story. Recall that the pharmaceutical industry stepped into this field 25 years ago when it appeared that nutritional therapy was not up to the task (at least as it was conceived at the time). If this protein hypothesis is correct, then better nutrition could be a much better form of prevention than pharmacotherapy. However, I suspect that the pharmaceutical industry will not back out of the field as readily as it got into it.

To be fair, resistance from big Pharma should not be surprising. After all, they've invested billions of dollars in helping us solve a critical health problem for an aging population. Naturally, they (and our pension funds who are their stockholders) want to protect that investment. Still, if diet can do the job for us, few would choose a lifetime of pill taking or injections over better eating.

This blog would be incomplete if I did not call attention to the fact that bone structure and density are designed by natural selection to resist mechanical loads, in other words, to permit a person to do physical work. In the absence of continuous mechanical loading, there is no diet, by itself, that will allow an older adult to regain the bone he/she had as a child. So, yes, calcium is important. And protein is important. But physical work is important, too. How much Ca? – probably 1500–1800 mg/day. How much protein? – probably at least 1.2 g/kg body weight/day. How much exercise? – probably about what the cardiovascular exercise people recommend, with special emphasis in this instance on impact exercise, such a jumping rope. Look at toddlers. Look at the impact forces to which they subject their skeletons. That's how they grow bone.

Posted in Calcium, Nutrient intake requirements, Nutrition, Vitamin D | Tagged bone, bone loss, calcium, nutrient effects, osteoporosis, protein, vitamin D | Leave a comment

Vitamin D and the nursing mother

Posted on June 5, 2014 by Robert P. Heaney
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Do infants receive enough vitamin D?

Everyone seems to agree that vitamin D is important throughout life. This is certainly as true in the first year of life as it is later on. For it is during the first year that, in addition to its role in calcium metabolism, this critical nutrient reduces both the risk of current infections and the late-life development of such autoimmune diseases as multiple sclerosis and type 1 diabetes. Both the Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP) agree that vitamin D intake during the first year of life should be 400 IU/d. My own estimation of the requirement (for different ages and body sizes) is 65–75 IU/kg body weight per day. For average body weights in infants during the first year of life that rule of thumb computes to somewhere between 300 and 500 IU/d for infants. So, while there is still contention with respect to the optimal intake for adults, there really is no disagreement about how much is needed for infants, either among various authoritative sources or arising from different approaches to the evidence. With respect to infants, 400 IU/d seems to be just about right.

The question is, how is the infant to get that vitamin D? Human milk, in most nursing mothers, contains very little vitamin D. Infant formulas, from various manufacturers, all contain some added vitamin D in amounts calculated to be sufficient to meet an infant's needs. But extensive studies during the first year of life reveal that less than one-fifth of all infants ever get as much as the recommended 400 IU/d from any source, and fewer than one out of 10 breast-fed infants meet the requirement. As a result, the AAP urges that all infants, regardless of whether they are breast or formula fed, receive their 400 IU/d as pediatric drops. Unfortunately, this recommendation, while appropriate, is not often followed. Most babies are

just not getting the vitamin D they need. The late-life consequences of this shortfall could be enormous.

It must seem strange that on the one hand we stress that human milk is the best source of nourishment for our babies, and on the other seem to ignore the fact that human milk doesn't contain the vitamin D those babies need. The explanation, very simply, is that the disconnect is artificial. Nursing mothers have so little vitamin D in their own bodies that there is little or none left over to put into their milk. But it has not always been this way. We know that the vitamin D blood concentrations that are regularly found today in Africans living ancestral lifestyles are high enough to support putting into breast milk all the vitamin D an infant needs. But the bulk of the world's population today is not living on the high equatorial plains of East Africa nor exposing much of its skin for most of the day.

Fortunately, we don't have to return to East Africa. It turns out that, if we give nursing mothers enough vitamin D to bring their blood levels up to the likely ancestral levels, then they automatically put all of the vitamin D their baby needs into their own milk, thereby ensuring that the infant gets *total* nutrition without the need to resort to vitamin D drops.

How much vitamin D does the mother need so as to ensure an adequate amount in her milk? As with everything else related to vitamin D, there is a lot of individual variation, but it appears that the daily intake must be in the range of 5,000–6,000 IUs. As no surprise, that's just about the amount needed to reproduce the vitamin D blood levels in persons living ancestral lifestyles today. And while 5,000–6,000 IU may initially seem high, it is important to remember how much the sun produces for us. A single 15 minute whole body exposure to sun at mid-day in summer produces well over 10,000 IU.

There is one important *proviso* for nursing mothers concerning the needed intake. Those who live in North America and have to rely on supplements should be certain that they take their supplements every day. While for other purposes it is possible to take vitamin D intermittently (e.g., once a week), that doesn't work for putting vitamin D into human milk. The residence time of vitamin D in the blood is so short that, if the mother stops taking her vitamin D supplement for a day or two, vitamin D in her milk will be low (or absent altogether) on the days she skips.

There is a glaring disconnect here between these well-attested physiological facts and the official IOM recommendation for nursing mothers, i.e., only 400 IU/d – the same intake for her as IOM recommends for her baby (whose body weight is less than 10% of her own). The IOM, if it were to be explicit about its current recommendations, would be telling nursing mothers something like this:

"The evidence we analyzed indicates that your own body needs only 400 IU of vitamin D each day. Unfortunately, that won't allow you to put any vitamin D into your breast milk. Sorry about that . . . So, if you want to ensure that your baby is adequately nourished, you are going to have to resort to giving your infant vitamin D drops."

That would be a hard message to sell, and clearly, it makes little sense on its face. As I have already noted, women living ancestral lifestyles (whether or not they are nursing an infant) have far higher blood levels of vitamin D than contemporary urban Americans. Milk production (and its optimal composition) are simply two of the many functions that vitamin D supports in a healthy adult. This breast-feeding example is not a special case; it is just one of

the many pieces of evidence that point to the fact that current vitamin D recommendations for adults are too low – way too low.

Vitamin D supplements – and in this case vitamin D drops – are literal lifesavers for infants today. But what about two or three generations back – before nutritional supplements come into existence, but long after migration out of Africa? Ninety years ago vitamin D had not yet been discovered, and there certainly were no vitamin D supplements that could have been used. How did we get by through those thousands of years? There are two answers. Most of us, living in temperate latitudes, got a lot more sun exposure than we do today, and of course there were no sunscreens, so there was no blocking of the solar radiation that produces vitamin D in our skin. Those of us living in far northern latitudes survived mostly by depending upon diets that were very high in seafood, which is naturally a rich source of vitamin D. And those of us who got vitamin D by neither route were at increased risk of a whole host of vitamin D-related disorders, most obvious and most easily recognized being rickets.

The bony deformities of rickets were common a century ago in Europe, North America, and East Asia, and were largely eradicated in growing children by use of cod liver oil and, in the US, by the introduction of vitamin D fortification of milk in the 1930s. Fortunately, growing children can repair some of the bone deformities of rickets if they are given vitamin D soon enough. But, repairing rickets, while a good and necessary thing to do, is not sufficient. It is too late, by the time we recognize the deformities of rickets, to ensure maximal protection against the autoimmune diseases (for example), for which susceptibility is mainly determined in the first year of life.

To sum up, we now better recognize the importance of vitamin D in the earliest stages of life. Furthermore, there is, as noted earlier, quite good agreement on how much an infant needs. Where we lack consensus is how to make certain that all of our babies get the amount they need. Why not rely on giving nursing infants vitamin D drops, as the AAP recommends? Two reasons: 1) It's been tried and has failed; and, 2) When it does work in individual infants, it provides no benefit for the mother. By contrast, ensuring an adequate vitamin D input to the mother during pregnancy and lactation is almost certainly the best way to meet the needs of *both* individuals.

An "adequate" intake for nursing mothers, as noted earlier, is not the 400 IU/d the IOM recommends, but is instead in the range of 5,000–6,000 IU/d, taken daily. If they get that much, they will meet not only their own needs, but their infant's as well. And they will have the satisfaction of knowing that they are supplying all their baby's needs, the natural way.

Links for more exploration:

1. Perrine CG, Sharma AJ, Jefferds MED, Serdula MK, Scanlon KS. Adherence to vitamin D recommendations among US infants. *Pediatrics* 2010;125:627-632.
2. Hollis BW, Wagner CL. The role of the parent compound vitamin D with respect to metabolism and function: why clinical dose intervals can affect clinical outcomes. *J Clin Endocrinol Metab* 2013;98:4619-4628.
3. Luxwolda MF, Kuipers RS, Kema IP, van der Veer E, Dijck-Brouwer DAJ, Muskiet FAJ. Vitamin D status indicators in indigenous populations in East Africa. *Eur J Nutr* 2013;52:1115-1125.

Posted in Nutrient intake requirements, Nutrition, Vitamin D | Tagged infant nutrient requirements, nutritional deficiency, pediatrics, vitamin D | Leave a comment

Antagonists or Partners? Part 2

Posted on March 25, 2014 by Robert P. Heaney
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In my last post I argue that capitalism and socialism need not be opposed to one another, as capitalism is focused mainly on increasing resources or wealth, while socialism is focused more on their distribution. However, as encountered in the real world, capitalism usually involves private ownership of resources while socialism often involves, instead, group or state ownership and management. Thus, if the frame of reference is ownership or management, the two could well be seen as opposites, if not necessarily antagonists. In any case, rather than focusing on labels ("capitalism", "socialism"), it will be helpful, instead, to concentrate on how the two economies operate.

Capitalism, it was noted, increases resources or wealth by feeding back some of the output of a productive process to improve its yield. Also, to ensure that this happens, built-in incentives seem to be needed. In theory, there is no reason why such improvement-oriented feedback could not work when resources are collectively owned. However, abundant experience with such approaches (U.S.S.R., Albania, Communist China, North Korea – to cite just a few modern examples) shows that collective ownership does not increase the size of the pie. There are several likely reasons:

1. Innovation is a "micro" activity and tends to be stifled at a "macro" level;
2. While the common good should motivate the members of a collectivity to improve its processes, opinions about what is worth doing or what is of value are not uniformly shared; so the enthusiasm, the extra work, and the consensus needed to implement or to test a change in process is weakened; and
3. As collective ownership often leads to the aggrandizement of power and wealth in the hands of a ruling class, little or none of the output of the economy is fed back in, so as to improve yields and hence increase the size of the pie.

Thus private ownership and management would seem to be an essential feature of an economic system that ensures the growing of the pie. However, that is a pragmatic rather than a deductive conclusion. One recalls the conclusion of Thomas Aquinas to the effect that he could find no philosophical basis for private ownership, but nevertheless supported it because he noted that resources are better managed when held by individuals than when held in common. One is reminded also of what Garrett Hardin more recently referred to as the

"tragedy of the commons". With that in mind, and taking our clue from Aquinas, it has to be said that control of resources needs to be seen not so much as absolute ownership but as stewardship.

I noted in the earlier blog that the way resources are distributed expresses, *de facto*, the values of a society. Whether based in economic pragmatism or religion, these values boil down to the degree of responsibility the members of a society feel toward one another. At one extreme, we have the shared care and concern of members of a closely knit family, and at the other, an every-person-for-himself mentality that inexorably results in greater and greater disparities between the "haves" and the "have nots". This latter is often referred to as *laissez-faire* capitalism. "*Laissez-faire*" is French for "let them do" (more or less as they please). It is important to stress that it is not an integral part of capitalism. The *laissez-faire* philosophy boils down to reduction or elimination of all external constraints on economic activity, i.e., little or no regulation.

The current debate in the United States, in which the terms "capitalism" and "socialism" are bandied about as epithets, is really about regulation, not about abstract economic principles. Regulation is not anti-capitalist, and does not in itself kill the process improvement which is the strength of a capitalist system. Nor does it necessarily stifle the incentive needed for the system to work. Thus to label regulation as "socialist" is nonsense. Perfectly good examples of constructive regulation exist in the contemporary world. Germany is a highly successful capitalist economy (and one we obviously admire, as judged from the tenor of television commercials), and yet the disparity between the haves and the have nots in the German economy is vastly smaller than in the United States. This is partly because the interests of the employees in big companies are required to be represented at the level of the board of directors of the corporations concerned. With that arrangement, both management and labor have a chance to see that what is good for both is good for the company. The necessity of regulating such arrangements is virtually self-evident: all the companies in an economy have to play by the same rules. The only feasible way to ensure that is to impose those rules from the top. George Tyler, in his book, "What Went Wrong . . ." describes two variants of capitalism, which he calls family capitalism and shareholder capitalism. Both are equally capitalist. They differ mainly in the sets of regulations under which each operates.

I mentioned above that the choice of systems of distribution might be based in economic pragmatism or in religious principles. It may be worth expanding a bit on each.

An economy must have both producers and consumers, and under ideal circumstances most members of a society would play both roles. That was the insight of Henry Ford who, as noted in the earlier blog, understood that his workers needed to be able to afford (and to buy) his automobiles. When wealth is so concentrated at the top of the economic ladder that those lower down have little or no purchasing power, then the economy will sooner or later – but inevitably – grind to a halt. It is a self-defeating situation and hence one that cannot be sustained. Expert economists and political scientists have noted also that democracy itself depends upon a society's having a large middle class. That is almost surely a part of the reason so many underdeveloped nations have had trouble accepting and integrating a political system that we in the U.S. consider ideal. Political power inevitably attaches to concentration of wealth, and when that happens the lower class majority no longer has effective voice or influence. We have at best an oligarchy, i.e., rule by the few. The ancient Greeks, who created the first true democracy, coined the term "oligarch", and Aristotle, himself, spoke of its disadvantages for a society over 2,300 years ago.

Religion does not speak with a single voice on these issues, but perhaps the most pertinent insights in this regard are found in the Jewish and Christian traditions, in which ownership of all resources is ultimately held by God, and in which the human role is as a manager or steward. (Obvious questions are: Management for what purpose? Stewardship for what end?) It is clear that a steward can abuse his or her control, as gospel parables clearly illustrate. Still the chemistry of stewardship – the attitude toward resources – is vastly different from that of absolute ownership.

Christianity adds another dimension to the Jewish understanding of stewardship. Very simply, baptism is seen as entry into a new family, with God as Father – a family not only with privileges, but with responsibilities as well. Early Christians – and we today – pray "*Our* Father . . .", not "*My* Father". Jesus said "You are all brothers [and sisters]" (Matt 23:8). Everyone within this kinship (and to whom we refer when we say "our") is brother or sister to me. I am called/expected to use my resources not only for myself, but for them as well – for them first, actually. That was immediately evident in New Testament times, in a culture where kinship established one's identity, and kinship obligations were paramount. Not everyone in a pluralistic society today necessarily buys into this understanding. Still, for those who call themselves Christian, it is a contradiction for them to ignore their responsibility to brothers and sisters.

Economics through the eyes of a whole organism physiologist

Posted on January 7, 2014 by Robert P. Heaney
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Antagonists or Partners?

There are two principal hormones that influence the concentration of sugar in the blood, insulin and glucagon. Insulin, familiar in the context of diabetes, lowers blood sugar, while glucagon, less well known, raises it. Beginning students are tempted to consider the two as antagonists, since they have opposite effects on blood sugar. But that is a mistake, as the concentration of these hormones in the blood is the wrong frame of reference.

Sugar (glucose) is the fuel that many tissues use to power their metabolic work, and insulin facilitates the entry of sugar into those cells or, in other words, insulin shifts some of the sugar from the blood into the tissues so they can use it. Inevitably, therefore, blood sugar concentration drops and could fall to dangerously low levels if it were not replaced. Here is where glucagon comes onto the scene. Glucagon converts sugar precursors stored in the liver into glucose, which then enters the blood, thereby replacing the sugar that was taken up and used by the tissues. Thus, rather than being antagonists, the two hormones work as partners getting the needed sugar into the tissues that depend upon it, and keeping it coming.

I thought of this parallel from physiology when, a few weeks ago, Pope Francis issued his first major communication, *Evangelii Gaudium*. In it he criticized some of the features of the way the capitalist economy, so dominant in our world, operates. (It is noteworthy that his predecessors had issued even stronger criticisms.) Francis' remarks were interpreted by several commentators as being "socialist" or "Marxist". It is as if, like insulin and glucagon, socialism and capitalism were somehow opposed to one another – *had* to be opposed. It's something everyone "knows". But, as with insulin and glucagon, much depends upon your frame of reference.

In brief, capitalism is a system which increases the size of the "pie". It is the best such system for doing this that we know of. And, with a growing world population, increasing the size of the pie is clearly an important thing to do. Socialism, by contrast, is concerned mainly with distributing the pie. As with glucagon and insulin, the two systems need to be seen as partners, working in concert with one another – capitalism making more available, and socialism, distributing it in accordance with a society's values.

What, in the last analysis, is capitalism? What is it about capitalism that enables it to increase the size of the pie?

It is surprisingly difficult to find a good definition of this thing that everyone talks about – capitalism. I do not believe it would be appropriate to characterize it by simply describing everything that goes on in the current world economy since, as we shall see, much of that activity, while enabled by, or growing out of capitalism, is not integral to it. The best definition that I have been able to find is simply that capitalism is a system of production in which some of the output of that system is fed back into the system to make it more efficient. And, by "more efficient" I mean that a given output requires less input, e.g., less effort, energy, or resources. Or, to put it the other way about, for the same input, the system produces

a greater output. There is a further feature of such a system that, while not integral to capitalism *per se*, is essential for it to operate as just described. That is incentive. There has to be some motivation, and given human nature as we know it, that means that the innovator must share in the productivity gains his/her innovation produces.

As I mentioned above, not all of the activities that we observe in the operation of our economy exhibit the features integral to capitalism. Today's corporate mergers might be one example of how capitalism operates, inasmuch as the merged companies can produce the same output with less input (e.g., less middle and top management or better purchasing power to acquire the input resources).This seems to have been the case, for example, with airline mergers, whatever else one may think of them. By contrast, corporate raiding would not be an instance of capitalism, inasmuch as nothing is produced by the raid. It is simply brigandage in modern dress.

One of the input costs to any human production process is, obviously, labor – employment – people. The replacement of people by robots in manufacturing is, once again, an example of capitalism playing out in accordance with its inexorable logic. Robert Reich in his book *Super Capitalism* cites examples of company after company that chose to do what they considered the "right thing" for their employees, i.e., putting their interests on the table as corporate strategies were developed and implemented. Clearly that would work fine if everyone played by the same rules. But if there are no rules, then companies making those employee-oriented decisions inevitably lose out to their competitors who are able to put their product into the market at lower cost than the pro-employee companies. As Reich points out, the market ultimately drove even those pro-employee companies to adopt the same brutal tactics as their competitors. The key point there is "playing by the rules". Rules, in some quarters, are considered destructive of the power of capitalism to grow the pie, or even an instance of what is denigrated as socialist. But that is absurd. All social organization needs rules. You can't simply drive on whichever side of the road you choose. You can't go on red and stop on green. The operation of the economy – any economy – is no exception.

In a very real sense employment is not only a cost of organized effort; it is, as well, one of its outputs or purposes. This may seem surprising, and even, to some, unacceptable. Nevertheless it is not "anti-capitalist", for the enterprises operating under a capitalist system can certainly choose to optimize human employment just as, in a different sense, they optimize physical product. It is worth remembering that perhaps Henry Ford's greatest insight was the realization that his employees could be his customers. He was certainly not a flaming liberal. Nevertheless, his corporate strategy is a notable instance of how employee purchasing power can be one of the outputs that can be optimized in a capitalist enterprise.

It is too often forgotten that one of the purposes of social organization (e.g., government) is precisely employment. From the time of the Pharaohs onward, a major objective of government has been employment (that and war). That is probably close to what Calvin Coolidge meant when he famously said "The business of government is business". Without business, there can be no employment, and without employment, the citizens of a country have no purchasing power, and that means no access to all the necessities of life. But this is not inevitable and cannot be accepted as such. As the Jesuit order stressed at its 1974–1975 General Congregation, "We can no longer pretend that the inequalities and injustices of our world must be borne as a part of the inevitable order of things".

To circle back to where we started, if glucagon and insulin can be thought of as rough counterparts of capitalism and socialism, respectively, the first thing one notes is that the body

regulates both processes. It needs both, but it cannot prosper if one or the other runs unfettered. There are tumors of the pancreas (where both hormones are made) that can produce an excess of one or the other, bypassing the body's regulatory controls. When that happens disease results. Any discrete population, such as a country, can be thought of very much like a body. Its smooth running requires controls. Too much regulation is bad, as well, and the trick, as always, is to find the middle road. And, as with physiology – to use the correct frame of reference.

Posted in Uncategorized | Tagged capitalism, Pope Francis, social justice, socialism | Leave a comment

Pellagra and the Four Ds

Posted on November 18, 2013 by Robert P. Heaney
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2014 marks the 100th anniversary of the war on pellagra, a war that lasted nearly 25 of those years before victory could finally be declared. You have not heard of the war on pellagra? The celebration is not on your calendar? You're not alone.

Why did it take so long? Was the science so intractable, like the current "war" on cancer? No. It was politics and pigheadedness that were the obstacles.

What is Pellagra?

It was in 1914 that Dr. Jozef Goldberger, a Hungarian-born, U.S. educated epidemiologist, was assigned by the U.S. Public Health Service to investigate an epidemic of a disease disabling and killing hundreds of thousands of U.S. citizens, especially in the southern part of the United States. The disease was pellagra, a word with Italian roots, meaning sour or rough skin, a reference to the dermatitis that is one of the hallmarks of the disease. Pellagra, we know today, is a nutritional deficiency disease, caused by diets poor in niacin (or its equivalent, nicotinamide). Niacin was the third of the B complex vitamins to be identified and so was given the designation "vitamin B_3". Niacin is critically important for essentially every cell in our bodies. It is a part of the biochemical machinery that captures and channels the energy produced when sugars and fats are "burned". That energy powers all cell work, from muscle contraction to nerve function to simple everyday maintenance of cell integrity. Thus it is easy to understand how deficiency of this vital molecule could produce total body disease.

Pellagra was characterized by the "four Ds" – dermatitis, diarrhea, dementia, and death. It is a perfect example of a point made in earlier posts in this blog that most tissues need most nutrients, and that a deficiency of virtually any nutrient impairs virtually every function of the body. This is in contrast to the popular belief that one nutrient may be good for the skin, another for memory, another for the eyes, another for the immune system – on and on – which is simply not accurate.

What is its Cause?

But pellagra is interesting and instructive for other reasons as well. Pellagra had been recognized for a couple of centuries prior to Goldberger's work, and there were varying theories as to its cause or what to do about it. Some medical experts thought it due to poor diet, others to infection or poor sanitation, and still others to toxins from food spoilage.

Whatever its basis, pellagra prevalence had increased alarmingly in the southern U.S. at the turn of the 20th century and something needed to be done to stop it. When Goldberger was assigned the task, the majority view in the U.S. seemed to tilt toward an infectious cause. The choice of Goldberger itself probably reflected that view, as he had earlier distinguished himself in epidemics of indisputable infectious diseases – yellow fever in Cuba, dengue fever in Texas, and typhus in Mexico City.

Epidemiologists, you know, have classically examined disease outbreaks to try to figure out how and why they happen – not just their cause, but why here? and why now?. In this case Goldberger quickly recognized that, in addition to its prevalence in the rural south, pellagra was common also among the inmates of northern institutions – orphanages and mental asylums particularly. But he noted a peculiar feature of those disease pockets – the institutional staffs did not develop it. Goldberger knew from personal experience that infectious outbreaks rarely discriminate between the keepers and the kept. He, himself, had succumbed to yellow fever, dengue, and typhus when he had investigated those epidemics. The one feature by which inmates and staff clearly differed in the northern institutions was diet, suggesting to Goldberger that poor diet was the likely underlying cause.

Nutritional deficiency was not an accepted category of disease when Goldberger started work. As I have noted in earlier posts, the prevailing view in medicine at the time was that, if you ate enough to perform daily work, you were adequately nourished. The idea that *not* eating something could make you sick was considered nonsense. Thus Goldberger had to overcome an immense amount of disbelief and resistance, and it is hard for us today to grasp all he had to go through. For example, he got grants to improve the diets of institutional inmates, which promptly cleared the pellagra. But when the grants were used up, institutional diets reverted to their prior, inadequate status, and pellagra reappeared. No one seemed to pay attention – not the institutional officials, not the government, and certainly not organized medicine.

What was it about the diet of individuals who suffered pellagra that was the basis for the niacin deficiency? Southern sharecroppers, particularly when economic times were hard, lived on what were called the three Ms – "meal, meat, and molasses". The "meal" was *corn*meal and was the basis for corn bread and grits and other such typically southern foods. The meat was not, in fact, a good source of protein, as it was fatback, providing mostly fat calories. And the molasses, likewise, provided mostly a source of sugar calories.

You may wonder about the cornmeal. What we in the U.S. call corn (technically maize) is a New World plant and was the principal cereal grain used by Native Americans up and down the length of the Western hemisphere. Surely they did not all suffer from pellagra. And, in fact, they did not. The reason is that they processed the kernels of corn differently from the way Old World immigrants did their milling.

All cereal grains have to be milled in order to remove the less edible parts, thereby producing flour which can then be cooked in a variety of ways. The niacin necessary to prevent pellagra (along with the other B vitamins), is concentrated primarily in the germ of the corn kernel (and the wheat kernel, as well). The milling practices used by Caucasians both in America and in southern Europe (to which maize had been imported), effectively removed the niacin from the cornmeal, just as similar practices with rice removed thiamine (vitamin B_1), leading to the disease, beriberi (which was epidemic in Southeast Asia a decade earlier). By contrast, Native Americans soaked the corn in lime water before milling, a practice that released the niacin and allowed it to be carried over into the flour during the stone grinding that the Indians used

to make flour. Thus the European milling practice produced a cornmeal that was bereft of its niacin, whereas the Native American milling did not.

The Opposition Grows

Goldberger, convinced that diet was the culprit, conducted an experiment in a Mississippi prison farm, exposing prisoners to a diet like those eaten by people manifesting pellagra and – no surprise – they developed pellagra within a few months. Medical experts claimed that it wasn't real pellagra and found other imaginary flaws in the project. Goldberger then went on to inoculate himself, his wife, and his assistant with blood and throat scrapings from pellagra patients – a test of the infectious hypothesis. But to no effect. He transferred skin scrapings and even fecal samples to healthy volunteers. Sometimes the recipients got temporarily sick, but they did not get pellagra. It simply was impossible to "catch" the disease. Still no one paid attention.

In fact southern politicians actively resisted the conclusion that diet was the culprit, fearing that the high prevalence in their states would cast their region in an unfavorable light if the disease was caused by poverty. They could accept infection (over which they had little control), but not poor diet due to socio-economic factors – for which they could be considered responsible. This was not the first time politics tried to discredit science – and certainly not the last.

Victory at Last

The story does not have an altogether happy ending. Fifteen years after starting on the project, Jozef Goldberger died of kidney cancer. He had not yet been vindicated and there was still, despite all his work, a prevalent view that pellagra was an infectious disease. Happily, the work was carried on by nutritional biochemists at the University of Wisconsin who were able conclusively to demonstrate that insufficient intake of niacin or nicotinamide was the entire explanation for the pellagra problem. By that time the truth could no longer be evaded. Steps began to be taken, first at a state level, and then finally by the U.S. government itself, to ensure that certain cereal products (mainly white bread flour) would be enriched with B vitamins, and specifically in this case, niacin. Doing so did not solve the underlying poverty, but it did help the inadequate diets of those trapped in poverty. In the United States, at least, pellagra is a disease of the past – fortunately – and it is doubtful today that most health professionals would recognize it if a case happened to come to their attention.

Some readers, who have looked more deeply into these topics, may recall that there is an essential amino acid (one of the building blocks of protein), called tryptophan, which the body can convert into niacin to a limited extent (limited largely by how much tryptophan may be left over after using ingested tryptophan to replace body protein). So, if the meat eaten by the poor sharecroppers had been of good quality, they might well have avoided the niacin deficiency because they would have been able to make sufficient niacin, at least to blunt the more severe manifestations of the disease.

Comment

We who are the beneficiaries of these hard won victories can too easily take nutrition for granted. It is important to reflect, occasionally, on how we got here.

The enrichment of white flour, which grew out of the concern to eradicate pellagra in this country, is a good example of food fortification, i.e., the addition to foodstuffs either of components eliminated during processing (as in making cornmeal), or components that most human beings need but may not otherwise consume in sufficient quantity (technically "fortification"). Another major addition to cereal grain products, implemented as late as 1998, was folic acid, a vitamin necessary for normal fetal development (as well as for a number of other vital activities). But it was fetal development that was the principal stimulus, as folic acid deficiency is a principal reason for congenital defects of the nervous system, such as spina bifida and what are called, generically, "neural tube defects". This most recent fortification was done without much public fanfare, although there was a tremendous amount of foot-dragging involved. The Food and Drug Administration had waited a full 24 years after the first request from the National Academy of Sciences before mandating the addition of folic acid. And that was accomplished finally by political pressure, not by the persuasive force of the science.

As the human race becomes increasingly inactive, physically (at least in North America), we can no longer afford to eat the large amount of food that was necessary to fuel the hard physical work that prevailed as recently as our grandparents' day. For that reason, we have to be increasingly conscious of the need to consume products that are high in the necessary nutrients, simply because we cannot eat as much as we once did. It is for that reason that fortification of widely consumed products (such as bread), is an increasingly attractive means of preventing critical nutrient deficiencies. Sometimes this can be an emotionally charged issue, often criticized as unwarranted governmental interference or an invasion of privacy. This is a concern that all of us need to reflect on and become informed about.

Posted in Nutrition, Policy | Tagged nutritional deficiency | Leave a comment

Some Rules for Studies Evaluating Nutrient Effects

Posted on June 25, 2013 by Robert P. Heaney
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The field of nutrition is confronting a strange paradox. On the one hand, nutrients are substances provided by the environment which an organism needs for the optimal functioning of its various physiological systems. In other words, a nutrient produces an effect that would not happen in its absence, i.e., it is efficacious for some vital endpoint or outcome.

Against that background and over the past few years, there has accumulated a near mountain of studies reporting that particular nutrients (e.g., vitamins A, C, D, and E, calcium, and others) have little or no effect when tested in human subjects for certain endpoints or outcomes. Of course it could well be that particular nutrients, while active in one body system, may actually have no effect in others. Well conducted studies in those systems would then produce null results. But this is not a likely explanation for many of the failed studies, virtually all of which grew out of epidemiological or associational studies linking the nutrients concerned to various plausible outcomes. In this post I explore some of the reasons that might explain this seeming contradiction.

It is helpful to start with the dose-response relationship followed by most nutrients (See Defining Normal – Living on the Plateau). As has been noted in earlier posts, that relationship is best represented by an *S*-shaped (sigmoid) curve. When evaluating a

particular nutrient we need to have at least a rough idea of the shape and location of that curve along the continuum of plausible intakes of the nutrient concerned.

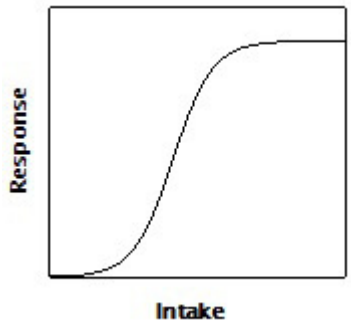

Fig.1. The sigmoid (S-shaped) response curve typical of most nutrients.

The curve in Figure 1 is a forward-leaning S-shape (sigmoid) and is typical for most biochemical reactions. Such reactions usually have three rough response zones: a no-response region at the left (which represents something like priming the pump – necessary but not yet enough); then a relatively steep rise up to some maximum response; and then finally a dose range in which further increases in intake produce no further response (which reflects saturation of the responding mechanisms). The forward orientation (higher response with greater exposure) is the usual way of graphing these effects, but a mirror image curve (high at left and low at right) is how negative effects such as risk or harm might be shown, i.e., the nutrient or drug *reduces* risk or *minimizes* harm as its intake increases. Figure 1, which is an idealized response curve, both makes clear what is meant by that statement and shows why it is important to test intakes in the response region of the curve (and not at either the low or high ends odf the curve). This is obviously necessary in order to optimize the chance of finding the response, if present.

Most drugs or biochemically active agents operate over an exposure range spanning three or more orders of magnitude; however, clinical studies evaluating their effects are commonly concentrated in the middle region where there is a near linear response to the increase in dose and hence its underlying sigmoidal character can be ignored. However, with nutrients, the entire curve is usually compressed within a single order of magnitude. (Examples include calcium, for which the 95% intake range extends from about 200 mg/d to about 2,000 mg/d, or vitamin D, for which the physiological range of serum 25-hydroxy-vitamin D extends from about 20 nmol/L to about 225 nmol/L.) The entire sigmoid curve of response to the nutrient is compressed within this range of plausible intakes. This means that the response to a given increment in intake from various starting values will vary. In fact, some starting levels will be either so low or so high that a substantial change in intake will produce either no response or one so small as to be hard to detect. This point is illustrated in Figure 2, in which an identical increase in intake produces very different responses depending upon where the basal (or starting) level of the participants is located along the response curve.

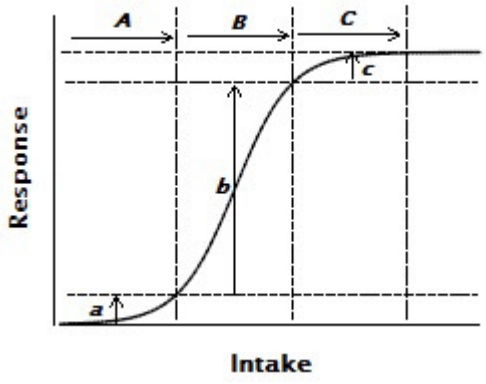

Fig.2. Three identical increments in intake are shown (A, B, & C), each starting at different basal status values. The responses elicited by each differ markedly and are shown as a, b, & c, respectively.

It is easy to see, therefore, why it is important to have prior knowledge of the shape and location of the curve and why it is important both to start at a basal level low enough to be at the left end of the curve and to ensure that all participants in a trial start at about the same level. Obviously, conducting a trial on individuals with different starting nutrient status values will blur the average response. If a nutrient does in fact produce the hypothesized effect, some subjects will nevertheless fail to show it, not because they are non-responders, but because either they started from such a low status that the dose was not sufficient to get them up to the response zone or, alternatively, they were already at or close to the maximum response.

And if most or all of the participants had starting values close to the top of the range, the trial would almost certainly be null because most or all of the involved participants would already be experiencing whatever response may have been hypothesized. One might ask, in the latter situation, "Couldn't one tell that the effect had already been produced?" The answer for quantitative response variables is "usually not". If the effect of an agent is, for example, to lower blood pressure by about 4 mm Hg, there would be no way to tell, against the background of wide variation in individual blood pressure values, whether participants' blood pressure values on entry had already benefitted from that average 4 mm lowering .

Establishing the basal level and using it as a criterion for entry into study is not just a minor quibble. Several large, government-sponsored trials over the past 15 years, costing millions of dollars, fell into exactly this trap and, not surprisingly, they produced null (i.e., no-effect) results. An example is the calcium arm of the Women's Health Initiative (WHI) trial. After the trial was fully enrolled it became clear that average calcium intake in the participants was already at or above the level recommended for their age. NHANES data, on which the WHI designers had relied, had shown that median dietary calcium intake of the target population was under 600 mg/d or about half the intake of the actually enrolled participants. The most likely reason for the discordance between expected and actual basal calcium intake was a combination of healthy volunteer bias and a failure to take into account the growing use of calcium supplements in the population. In any event, had the presumed calcium intake been operationalized as an inclusion criterion, the calcium arm of WHI would have provided a far better test of the related hypotheses.

What is harder to explain is why the results of this trial continue to be cited (and accepted) as evidence that calcium has no effect on the several outcomes that had been planned for analysis in WHI. Nor was WHI an isolated instance. Exactly the same mistake was made with

the calcium and preeclampsia prevention trial (CPEP) and its outcome, though for very different reasons.

Finally, studies may be null because of failure to optimize co-nutrient status. The importance of doing so can be illustrated by a few examples. It is well recognized that vitamin D is necessary for regulation of calcium absorption, but it is less well recognized that quantitative analysis of the relation makes clear that vitamin D follows the sigmoid curve of Figure 1, i.e., its effect on calcium absorption reaches a maximum. Above that point more vitamin D does not produce more absorption. It has further been shown that even maximal vitamin D status will not compensate for calcium intakes below a certain level, i.e., even maximal absorption of not very much ingested calcium will result in not very much *absorbed* calcium. Thus, when testing skeletal outcomes and evaluating the effect of either vitamin D or calcium, it is essential that intake of the nutrient not being directly tested be optimized. Otherwise the effect of the nutrient being tested may be missed. But it doesn't stop there. Protein is as necessary for bone repair as is calcium, and without adequate dietary protein, increased dietary calcium will not lead to replacement of lost bone, a fact that may help explain why many trials of supplemental calcium failed to increase bone mass. Several of the B vitamins (e.g., folate, B_6, B_{12}) are intimately involved in a biochemical process called single carbon transfer, and to discern the full effects of one, studies must ensure that intakes of the other two are not so low as to limit the response to the one being tested.

These examples are just that – illustrative. But they are not solitary instances. The one constant in nutrition is that isolated nutrient deficiencies are the exception. Diets inadequate in one nutrient are almost always inadequate in several others as well.

It is surprising how little attention is paid to the matter of making certain that nutrients other than the one being evaluated are present in adequate quantity. This is partly because of a reductionist approach which looks at nutrients in isolation, and partly because the drug model for evaluating pharmacological agents attempts to minimize and even eliminate, the impact of co-variates, while, as noted, nutritional co-variates must instead be optimized. Nevertheless this drug model has been carried over whole into the evaluation of nutrients without attending to critical differences between the two classes of agents.

The continued citing of studies that in hindsight could not have tested the corresponding hypothesis occurs most harmfully in approaches termed "systematic reviews" and "meta-analyses". Both involve search of the published scientific literature to find all studies bearing on a particular question and then selecting some of them for inclusion in the review. The selection criteria usually consist of whether or not the studies meet certain design standards such as randomization or blinding, among others. Few such reviews use biological criteria that included studies must meet. As a result, in reviews of calcium, e.g., they inevitably include studies such as the WHI calcium arm and CPEP which, as just noted, could not have tested the corresponding hypotheses. Accordingly, such reviews tend to produce null results. This seems part of the reason studies of so many nutrients mentioned at the outset continue to turn up without seeming effect.

Accordingly, systematic reviews and meta-analyses need to be concerned with the same issues important for individual studies and, importantly, to use as selection criteria for study inclusion, features based on the biology of the nutrient concerned and not exclusively on reporting features of the papers to be analyzed.

Inspection of Figures 1 and 2 makes clear that, even if all studies have the same basal nutrient status, different doses of nutrients will usually produce differences in responses that are not linear, a fact that makes statistical adjustment for dose problematic. Given the often narrow dose range between the bottom and top of the sigmoid curve, twice the dose (doubling the intake) will usually not produce twice the response. It may be more than double or it may be less, and it may even be zero if the smaller dose had already gotten the participants up to the top of the sigmoid curve.

But just as the response to nutrient augmentation is non-linear, so too is the response to duration of intervention. For many nutrients, therefore, studies of substantially differing durations cannot easily be pooled. For example, calcium supplementation evokes what is called a "bone remodeling transient" and measurement of bone mass or density will often produce an apparent rise at short time intervals (e.g., six months), a smaller rise (or no apparent change in bone mass at 12 months, and then after actual bone loss (though at a slower rate than without the supplement). The non-linear region of the response curve is usually confined to the first 12 months, when a new steady state develops. For these reasons, attempts to assess the ultimate effect of calcium intake must be confined to the steady state region of the response curve. Clearly, pooling studies carried out over different portions of the transient will yield confusing or misleading results.

Failure to pay attention to these biological issues, either in individual studies or in systematic reviews and meta-analyses, will inevitably bias the results toward the null, which is statistical jargon for reducing the apparent size of the effect to a point where it is not statistically significantly different from no effect at all.

It may be objected that we may not have the knowledge needed to attend to these matters, even if we had the will. That much is certainly true. However, there is a second purpose of this discussion: it allows us to understand why studies of actually efficacious agents might turn out null. And in the case of systematic reviews and meta-analyses, they should stop us from continuing to cite studies as evidence of a certain conclusion when, in hindsight, we ought to have recognized that these studies could not have validly tested the associated hypotheses. (Systematic reviews, basically, are simply a form of hindsight.) That mistake was a conspicuous feature of the systematic reviews relied upon by the Institute of Medicine and the U.S. Preventive Services Task Force in formulating their recent policy statements for calcium and vitamin D.

The Sodium Story

Over the years I have attended many official dinner events, usually seated next to people not previously known to me. When I would ask one of my table companions to pass the salt shaker, I would inevitably be greeted with, "You're a doctor! You know salt is bad for you . . ." It's something everybody seemed to know. Is it true? What are the facts?

First, we know that high blood pressure is common and that it is a potentially serious health problem, increasing risk of heart attacks, strokes, and kidney failure among other bad outcomes. It is also true that there are breeds of rats that develop high blood pressure when fed a high salt diet. And humans with high blood pressure will frequently experience a drop in blood pressure if they go on a low salt diet. It all seems to add up to a pretty compelling case against the presumed culprit – salt.

While the foregoing is accurate, it's only a part of the story. First, what we colloquially call "salt" is chemically, sodium chloride. Both sodium and chloride are nutrients. A nutrient is a substance the body needs for health but which it cannot make for itself. The reason sodium and chloride are essential is that our blood and body fluids are intrinsically salty – a reflection of the saltiness of the sea in which vertebrate life evolved on our planet. The body absolutely depends upon a certain degree of saltiness – anything appreciably more dilute or more concentrated is not compatible with life (let alone health). In maintaining the ideal concentration, the body regulates body water and blood volume up and down. Blood volume in turn is a major factor in maintaining normal blood pressure – which is the amount of force needed to pump blood to all the vital organs and to push it through the tiny blood vessels that nourish the billions of cells in our tissues.

Salt is at the very heart of this system. Salt, of course, is needed for saltiness. We lose salt every day in sweat, tears, and urine; and it has to be replaced. The role of salt intake is so central that all land-living vertebrates exhibit what is called a "salt appetite", meaning they are drawn to natural sources of salt – salt licks, brine pools, and the like, which abound in the landscape. Mark Kurlansky, in his fascinating book "A World History of Salt" notes that the early American pioneers, exploring the territory west of the Appalachian Mountains, didn't have to hack their way through dense forest. They simply followed the trails blazed by generations of wild animals leading to salt sources. That preference for things with a salty taste is driven not so much by the taste itself as by the animal's own management of its internal environment. When it senses a decrease in central blood volume, salt appetite increases; and when that volume is adequate, the drive to find salt abates. Exactly that same regulation occurs in modern humans and, while it is possible to develop a taste for salt that exceeds our actual needs (which is where the common perception that perhaps we get too much comes into the picture), it is also true that basically, our drive to eat salty foods reflects real need to maintain an adequate body salt content.

Not surprisingly, if you decrease salt intake and your body's content of salt drops, your blood pressure falls as well. That may be good if you have a very high salt intake or high blood pressure. But it's not automatically good for everyone. Nevertheless lowering salt intake lowers blood pressure to some extent in most people, not just those with high blood pressure or high salt intakes. When blood pressure falls or body water shrinks, the body attempts to compensate by producing chemical messengers that tighten up muscle tone in the walls of small arteries, that reduce water loss through the kidneys, and that restrict sodium loss in

sweat and urine. These responses help make certain that the most critical organs get the blood they need. But it's a band-aid measure that tides us over an emergency.

There should be no doubt: ***the body absolutely needs sodium***. The real question, as for most nutrients, is not whether it's essential, but how much is enough? How much is too little? And how much is too much?

Those "how much" questions for all nutrients are answered for us in the U.S. and Canada mainly by a quasi-governmental body called the Institute of Medicine (IOM), which periodically publishes recommendations for the intakes of all nutrients, based on its up-to-date evaluation of the continuously accumulating evidence. [Another source of related guidance is the "Dietary Guidelines for Americans" published every 5 years by the U.S. Departments of Agriculture and Health and Human Services.] Over the past 40 years both bodies have emphasized what they thought was the importance of reducing salt intake. This thrust dates back at least to 1972, when the recommendation was to "use salt in moderation". The pace quickened over the next 40 years with each successive set of recommendations, reaching a peak in the 2005 IOM recommendations, which called for keeping total sodium intake under 1500 mg per day for adults up to age 50, and under 1300 from age 50 to 70. To put these numbers in perspective, it's helpful to note that average sodium intake in the U.S. and much of Europe is between 3400 and 3600 mg per day, and has been constant at that figure for as long as it's been measured. So, if 1500 mg per day is the right number, then it's clear that we're all eating way too much salt. However, the fact that sodium intake hasn't budged despite massive public education campaigns (and the awareness of my dinner companions) suggests that this is the intake that "seems" right to our bodies.

Not widely recognized is the fact that the severely restrictive recommendations of the IOM have not elicited a consensus within the scientific community. Several years ago the editor-in-chief of the *Journal of the American Medical Association* was quoted in an article in *Science* as saying that these current recommendations "go way beyond the evidence". That was not a solitary dissent by any means, as other prestigious scientific journals have recently published editorials making the same point – namely that there was no evidence of benefit from such low intakes, and, in fact, no assurance that they were not actually harmful.

The 40-year era of attempting to reduce everyone's salt intake came to an end on May 14, 2013, when the IOM issued new guidelines for American salt intakes. Recent studies had provided compelling evidence that salt intake in the range recommended by the IOM in 2005 ***could actually increase heart-related illness and death***. So, in a dramatic reversal, the 2013 recommendation acknowledged that there was no evidence that reducing intake below 2300 mg per day was beneficial. It said that it thought U.S. sodium intake was still higher than it ought to be; however that statement seems to me to have been more a concession to the anti-sodium forces in the nutrition policy establishment, than an evidenced-based conclusion.

The reasons behind this shift can be briefly summarized as follows: The chemical messengers (hormones) that humans produce to throttle back salt losses from the body are compounds called renin, angiotensin, and aldosterone. These hormones begin to be produced in increased amounts when sodium intakes drop below about 3200 mg/d. The lower the intake gets, the more of these protective compounds is produced. These are what are called in physiology "rescue" mechanisms, which means they function to tide an organism over a temporary problem (as from sudden blood loss or dehydration), until the animal (or human) can access the salt and water it needs to restore central blood volume. In that sense, they're just like

adrenaline, which is also produced in times of stress (though of a different sort). They're both emergency tools, automatically deployed by the body in times of need.

The principal problem with the 2005 IOM recommendation (under 1500 mg sodium per day) was that, if followed, it would create a situation in which these rescue mechanisms were being constantly deployed. There has been evidence for years that sustained high levels of renin, for example, actually increase the risk of heart attacks and cardiac death, particularly in patients who already had heart disease. Until recently the IOM had simply focused on the blood pressure effects of sodium intake reduction – believing apparently that any decrease in blood pressure was good for you – and ignoring (or unaware of) the harmful effects of living 24/7 with high levels of the rescue hormones. Belatedly the emphasis has now shifted from blood pressure (with implications for health) to the actual health outcomes themselves.

Another problem with the 2005 IOM recommendations – indeed with most IOM nutrient intake recommendations – is that they treat individual nutrients in isolation. But, as I have noted in earlier posts, nutrients are like the instruments in a symphony orchestra. They play together and the totality is often more than the sum of the parts (see "Change your oil, Ma'am?"). It is known, for example, that increasing intake of calcium and potassium to levels closer to what our ancestors received (see "Defining Normal – Lessons from our ancestors") lowers blood pressure as much as does the most severe restriction of sodium intake. A small fraction of the modern human population has what is termed "salt sensitivity". Their blood pressure does go up as salt intake increases. But ensuring adequate calcium and potassium intakes minimizes or protects against this tendency, a fact that the anti-sodium bloc had ignored.

I have heard complaints about this recent IOM reversal, not so much from people who disagree – but from people who say "What are we to do? We thought we could count on the IOM to tell us what was right." The good news response is that science is a self-correcting enterprise. All we can tell you today is what we know today. And when we know more or know better, we will tell you that. Perhaps all along we should have communicated the inevitable tentativeness of any conclusions that we can draw. Unfortunately, people often want more certainty than the science permits. Also, scientists themselves are not always totally dispassionate or objective. It's easy to feel certain about something one cares deeply about, and scientists, being human, often are vocal advocates for one position or another. Sometimes it seems that the one who shouts the loudest gets his viewpoint adopted by the others. But in science, at least, that's only temporary. Sooner or later, as the impact of personality fades and the mass of the evidence grows, science rights itself.

Bottom line. For the average healthy person, be assured that your current sodium intake is probably OK. The U.S. average of about 3450 mg sodium per day is just above the point where the rescue mechanisms begin to kick in. So it's not too much by any means. On the other hand, an intake of 6000 mg/day or higher can increase your risk of developing high blood pressure. So 6000 is too much. If you have a medical condition and are under the care of a physician who has recommended reduced sodium intake, take his/her advice; you're paying for it. But, in view of the new IOM statement that there is no evidence of benefit for intakes below 2300 mg sodium per day, you might wish to ask your physician whether he/she is aware of the change and seek reassurance that continuing on a low salt diet is actually right for you.

Posted in Nutrient intake requirements, Nutrition, Policy | Tagged blood pressure, hypertension, Institute of Medicine, sodium | 2 Comments

PART FOUR: Defining normal – origins and resiliency

Posted on May 17, 2013 by Robert P. Heaney
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Part One: Defining normal - lessons from our ancestors
Part Two: Defining normal – thermostats, feedback and adaptation
Part Three: Defining normal – living on the plateau

In prior posts I have noted that nutrition policymakers lack a shared vision of "normal" and are forced, therefore, to fall back upon phenomenological or empirical methods to discern and justify nutrient intake recommendations. In those earlier posts I reviewed briefly three alternatives to this phenomenological approach. In this post I describe two additional methods which, in themselves, may not be widely applicable across the full array of essential nutrients, but which could offer persuasive support for recommendations derived from one or more of the previous three approaches.

Origins

The fourth approach to defining a nutrient requirement is, in a sense, a return to our biochemical origins. It is useful to recall that primitive organisms require very few nutrients. The chemistry of life depends upon a great many chemical compounds, but primitive organisms make most of them for themselves. They can't avoid dependence on the environment for minerals and energy (since neither can be made). But otherwise they are amazingly self-sufficient. There is, however, an energy cost to making the chemicals of life and most of the energy available to primitive organisms has to be devoted to making what they need to stay alive and reproduce, not to diversify or specialize. The amount they make is effectively equivalent to the amount they need.

When particular environments happen to provide one or more of the required chemical compounds, it is to the organism's advantage to stop making them for itself, and to depend, instead, upon its particular environment, which provides those compounds, ready-made. Thus, genetic mutations resulting in loss of ability to make a particular compound, while often deleterious, can actually be advantageous if the compound concerned is available in the environment. The mutant organism can divert to other purposes some of the energy no longer needed for day-to-day survival, allowing them to diversify and specialize. Over the millennia of biological evolution this process has enabled development of the immense array of living organisms, animal and plant – and ultimately the great apes and humans. Most animals today exhibit extensive dependence upon their environments to provide the chemical compounds they no longer make for themselves. It is these compounds that we call "nutrients".

How can we use these insights to get at an estimate of how much of those nutrients is needed? One approach is by measuring how much of a particular chemical compound a species' immediate ancestors made for themselves, just prior (in the evolutionary course of things) to the mutation that led to the first loss of synthetic capacity. This quantity is key, for the energy economy involved in natural selection guarantees that an organism making these compounds of life would not make more than it needed. One wouldn't need a time machine to find that quantity, since modern molecular biology is able selectively to breed animals in which particular genes have been inactivated. Such animals, lacking the ability to synthesize for themselves a particular essential substance will, therefore, develop a deficiency disease unless

the compound needed is supplied in the diet. The amount needed to restore *full* health is thus that animal's requirement.

Vitamin C is a perfect – if controversial – example. Vitamin C (ascorbic acid) is absolutely essential for life – so essential that most of the organisms in our environments make their own – most dogs, cats, rats and mice, etc. But somewhere along the branches of the tree of living species, a few animals and many of the primates – including *Homo sapiens* – lost that ability. The quantity made by the "highest" primate still making its own is an estimate not only of what that species needs, but of how much closely related species, such as humans, might need as well. Even without resort to the tools of molecular genetics, we can study modern mutants. There is, for example, a rat that lacks ability to synthesize ascorbic acid, a contemporary counterpart of an ancestral model animal. Available estimates of its requirement for externally supplied vitamin C are in the range of 30 mg/kg/day.

Of course, when taking this approach it is necessary to make allowance for differences in body size and a host of other factors, such as presence of other compounds able to fulfill vitamin C's functions. For this reason, precise estimates of the requirement for a particular nutrient may not be possible using this approach alone. Nevertheless, even rough estimates can be useful. For example, if the primate closest to humans made a body size-adjusted 2000–3000 mg of vitamin C daily, it would seem unlikely that the human requirement could be as little as just 2% of that figure. Actually, the official RDA for vitamin C for adult women is exactly that: 60 mg/d (or 2–3% of what may have been the ancestral utilization). Incidentally, the current 60 mg figure reflects only the amount needed to prevent scurvy, not the amount needed to optimize the many metabolic functions of the vitamin. Experts in vitamin C biology have long maintained that simple prevention of scurvy was not the right criterion for nutrient adequacy, that scurvy was actually the manifestation of only the most extreme degrees of vitamin C deficiency, and that its absence, was therefore not the best criterion of adequacy.

Resiliency

The final approach to estimating nutrient requirements is resiliency, or what, in physiology, is termed homeostasis – i.e., the ability of the body to maintain (or restore) a normal value for the various components of our internal environments. As noted in earlier posts, the ultimate function of nutrition is the support of physiological functioning, i.e., ensuring that our bodies have enough of a given nutrient so that a particular physiological process is not limited by nutrient availability. Hence, this issue of resiliency is, in concept, absolutely central to the issue of "normal" nutrition. Can we tap it to gain insights into nutrient requirements?

Tests of resiliency are familiar in the practice of medicine, if not currently used in nutrition. The cardiac stress test is one example. Cardiac response to increased demand for oxygen (induced by walking rapidly on a treadmill) is monitored. The response of the heart to the extra work and the changes it makes to support that work are measures of cardiovascular resiliency. Similarly, a glucose tolerance test involves a deliberate elevation of blood sugar; the test then monitors both how rapidly the body can restore blood sugar to acceptable levels and how much insulin it takes to do that (as well as the ability of the pancreas to put out the needed insulin).

To the extent that various physiological activities may be measurably dependent upon nutrient availability, comparable tests can be devised in which, for example, response to a standardized depletion of the nutrient concerned is measured – reflecting both the status of the

nutrient reserve and the availability of redundant or alternative mechanisms to compensate for the induced deficiency.

Because responses to perturbations of homeostasis will almost always involve multiple pathways spread across several body systems, capturing and characterizing these responses will likely be possible only by using the emerging science of metabolomics, still to be widely applied to the understanding of nutrient deficiency. Such responses might involve, for example, changes in concentrations of biomarkers of oxidative stress or inflammation, among many others (such as altered gene expression). This is still largely unexplored territory, so of little immediate applicability to nutritional policy. Nevertheless it would seem well worth exploring. Further, altered "-omic" patterns are likely, in themselves (and even without prior perturbation in some kind of test), to reflect relative nutrient status and might thus be helpful in defining "normal".

Conclusion

In this four-part posting I have described five possible, physiology-based approaches to defining "normal" nutrient status – something that the currently employed phenomenological approach cannot do. Some of these approaches, for at least some nutrients, are ready to use today. Others will require development. All seem worth pursuing.

Nutrition is important – more important than many health professionals seem to believe. The public understands that importance.

Posted in Nutrient intake requirements, Nutrition, Policy | Tagged vitamin C, what is normal | Leave a comment

PART THREE: Defining normal – living on the plateau

Posted on April 18, 2013 by Robert P. Heaney
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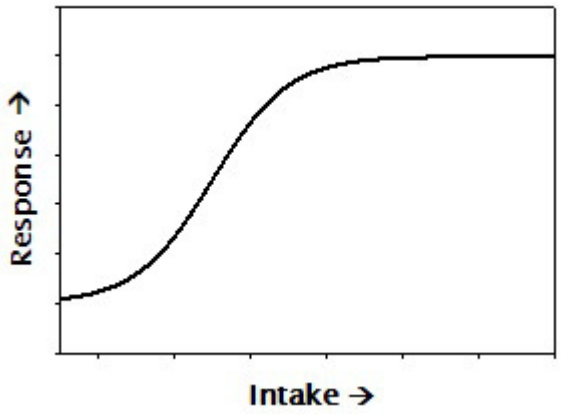
Part One: Defining normal - lessons from our ancestors
Part Two: Defining normal – thermostats, feedback and adaptation
Part Four: Defining normal – origins and resiliency

In this post we pursue yet another way of determining a nutrient requirement.

A feature common to most (if not all) nutrients is the effect plateau. If you start from a state of nutrient deficiency, increasing intake of the nutrient concerned produces a measurable, beneficial change in some function or outcome that expresses the nutrient's activity. For example, if you have iron deficiency anemia and you start taking iron supplements, your hemoglobin and red blood cell count will increase. Your anemia will be treated and, in most cases, cured entirely. But there is a clear limit. Once your hemoglobin reaches normal values (about 14 g/100 mL of blood), no further increases can be produced by taking more iron – even if you double or triple or quadruple the dose. You have reached a plateau.



If you're losing iron (as with heavy menstrual flow), you'll need to take a maintenance dose of iron. A dose (actually, better: an iron *intake*) that is just sufficient to keep your hemoglobin up on its plateau is the intake that satisfies your body's need for iron. It is your "iron requirement". This behavior of hemoglobin in response to iron intake is depicted in the figure to the left, in which "intake" refers to iron status and "response" to blood hemoglobin concentration. The actual value of the requirement will vary from person to person and from time to time in an individual, depending on how much iron one's body is losing every day.

Because iron is a building block of the hemoglobin molecule, if you don't have enough iron you won't have enough hemoglobin – i.e., you will be anemic. The same is true for calcium and bone. A newborn human baby's body contains 25–30 grams of calcium. That mass will increase to 1000–1500 grams by the time the child reaches full adult status. All that additional calcium has to come in by mouth. If after weaning you rear experimental animals on diets with varying calcium contents, and measure how much bone they have when fully grown, you will get a curve that's exactly the same as the one shown above. And like iron, once you're on the plateau, extra calcium will produce no more bone.

This behavior is relatively intuitive for bulk nutrients such as iron and calcium. But it's also true for nutrients that are not so much *accumulated* by the body as *utilized* in helping the body perform some key function. Vitamin D, for example, helps the body regulate intestinal absorption of calcium from the foods in our diets. When a person is vitamin D deficient, calcium absorption will be impaired – i.e., it will fall somewhere along the ascending limb of the curve in the figure. But once you've raised your vitamin D status and have absorbed as much calcium as your body needs, increasing vitamin D status has no further effect. You've reached the absorptive plateau.

[Actually, vitamin D doesn't raise calcium absorption at all – as we once used to think. Instead, what it does is enable the body to increase calcium absorption when the body needs more calcium – but has no effect when the body has enough. That's why, once you're up on the absorptive plateau, no further absorption occurs. Knowledgeable readers will recall that there is a derivative of vitamin D, called calcitriol, which the body makes when it needs to augment calcium absorption and which does, indeed, increase calcium absorption directly (and essentially without limit). If you were to administer calcitriol – sometimes referred to as "active" or "activated" vitamin D – you would definitely increase calcium absorption, whether the body needed the calcium or not. But it's not the native vitamin D that's producing this effect. Dosing with calcitriol effectively bypasses the body's regulatory controls. The reason why normally the body does not increase calcium absorption as vitamin D intakes rise

is precisely because the body reduces its production of calcitriol once calcium absorption is adequate for the body's needs.]

While, as noted at the outset, this plateau effect appears to be common to most or all nutrients, there are some for which there isn't an easily measurable effect, and therefore no direct way to get at defining the effect plateau. Protein, for example, is necessary for growth and for increasing muscle mass during growth. Like other nutrients, once a person reaches the amount of muscle that's just right for his or her hereditary constitution and physical activity, more protein will not make more muscle. But muscle mass is difficult and expensive to measure – unlike hemoglobin (for iron). However, there is a potentially very useful substitute measure – plasma insulin-like growth factor-1 [IGF-1] – a member of the class of compounds called "biomarkers". IGF-1 concentration in blood does reflect protein intake and follows the rising limb of the curve above, just as does hemoglobin with iron. The IGF-1 plateau is not as well studied nor quite as precisely nailed down as some of the other relationships I've just reviewed. However the basic pattern – the plateau – seems to be the same as for other nutrients. More research is clearly needed. But available data indicate the IGF-1 concentrations begin to plateau at protein intakes in the range of 1.2–1.3 grams protein/kilogram/day, a figure that is about 50% higher than the current recommendation for protein intake.

For all nutrients for which we can define a plateau, the determination of the nutrient requirement – the "recommended" intake – follows directly from these behaviors. An intake sufficient to get 97.5% of a healthy population up onto the effect plateau is, manifestly, a defensible estimate of the requirement (specifically, it would be the RDA).

Interestingly, in its 2011 intake recommendations, the Institute of Medicine (IOM) used the plateau effect as a part of the basis for its recommendation for vitamin D. The IOM asserted that a 25(OH)D level of 20 ng/mL was sufficient to ensure that most individuals would be on the calcium absorptive plateau. Unfortunately, the IOM panel relied on absorption studies that did not use a nutritionally relevant calcium load. As a result they greatly underestimated the vitamin D status needed to guarantee optimal regulation of calcium absorption. This is seen immediately when we recall that absorption is a load phenomenon, i.e., how many ions of calcium can be carried across the intestinal mucosa during the short time during which the digested food is in contact with the absorptive mucosa. Vitamin D (actually calcitriol in this instance) causes the intestinal lining cells to manufacture calcium transporters. Clearly, if you have fewer calcium ions to transport, you can max out with fewer transporters. It's just that straightforward. As a consequence, it follows that if you want to optimize absorptive regulation for nutritionally relevant calcium sources (e.g., a glass of milk), you've got to do your testing using nutritionally relevant calcium loads. And when you do that, the absorptive plateau begins at 25(OH)D concentrations of 32–35 ng/mL, not 20 as the IOM declared.

PART TWO: Defining normal – thermostats, feedback and adaptation

Posted on April 8, 2013 by Robert P. Heaney
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Part One: Defining normal – lessons from our ancestors
Part Three: Defining normal – living on the plateau
Part Four: Defining normal – origins and resiliency

In this series of posts, I address the concern that clinical nutrition as a discipline, and the nutrition policy establishments in particular, have no shared concept of what is "normal" nutrition. This creates obvious difficulties in formulating and publishing recommendations for nutrient intakes. The approach currently in vogue is to presume that average intakes in the general population are adequate, and to require hard evidence that something more or less would be better. This despite the fact that the populations of the industrialized nations are beset with a myriad of chronic health conditions, piling up toward the end of life, and including such disorders as cancer, cardiovascular disease, atherosclerosis, obesity, osteoporosis, diabetes, dementia, and many others. Unavoidably, the individuals we take as our benchmark normal are, in fact, individuals in the incubation stage of one or more of these chronic disorders. Thus presuming that typical intakes are "normal" (i.e., optimally healthful) is clearly circular.

In my first post of the series, I suggested an alternative approach to the definition of "normal" as applied to nutrition, i.e., selecting the ancestral intake, the one that prevailed when human physiology was evolving. In this post, I offer yet another possible criterion, one that could be applicable to many nutrients. It might be called the "set point" criterion or perhaps better, the "least adaptation" criterion.

This suggested approach is based on the fact that many – perhaps most – physiological systems function at a status or setting that ensures that conditions are optimal for our physiology. We maintain those settings by control systems that operate around a set point. The number of such systems is legion, including thirst, hunger, blood pressure, blood sugar, body temperature, bone mass, the ionic composition of the various body water compartments, on and on.

Perhaps the most familiar example of such a system is the means whereby we regulate the temperature in our homes and work places. We have a device called a thermostat, and we set it to a certain temperature (the "set point"). If the temperature falls below that set point, then the heating system kicks in and pours heat into the system. Conversely, if the temperature rises above that setting, then the cooling system does the opposite. The colder the temperature outside, the more the heating system has to work. The downside of too much work by the heating or cooling systems is not just the extra energy cost, but the fact that the equipment, working harder and longer, wears out sooner.

All analogies limp, but this one is better than most, with our various body systems working almost exactly as I've just described. There's just one small difference: in our dwellings we are able to change the set point, while in our bodies we can't; they've been pre-set for us by the forces of natural selection.

Take for example the regulation of blood calcium concentration. For reasons that are not entirely understood, the concentration of calcium ions in our blood serum and body fluids is one of nature's physiological constants, with the same value being found across most of the vertebrate phylum (animals with a backbone or spinal column). The set point value for total serum calcium is about 2.4 mmol/L (9.6 mg/dL). In humans calcium is lost from the body in a variety of ways, and is gained by the body from absorption of the calcium contained in the foods we eat. The job of the regulatory system is to reduce the impact of those gains and losses on blood calcium concentration so that it doesn't vary appreciably in response to the inevitable variation in inputs and losses over the day. The body uses two hormones of the endocrine system to counter these fluctuations: for a fall in blood calcium, parathyroid hormone (PTH), and for a rise in blood calcium, calcitonin. These hormones are exact counterparts of the heating and cooling systems in our dwellings.

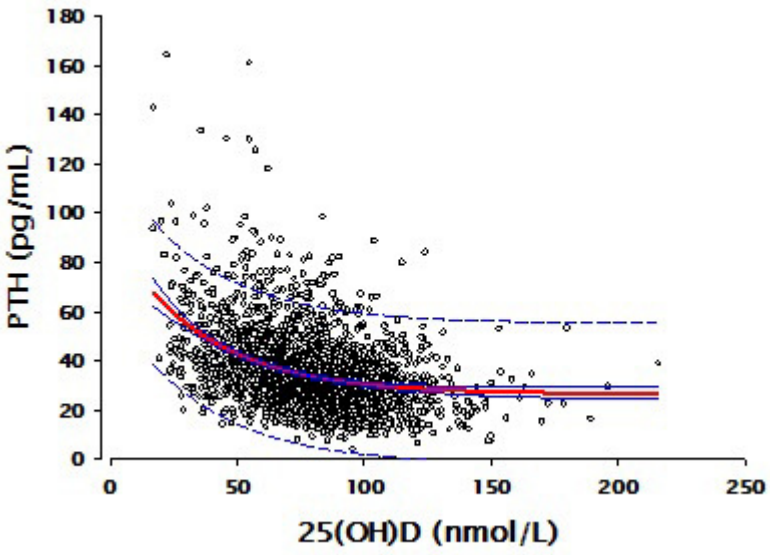
Under the environmental conditions in which human physiology evolved, calcium was a surfeit nutrient. For that reason, our intestines have evolved to block most calcium absorption. Only about 10–12% of diet calcium is absorbed unless we actively need more, at which point the endocrine control loops cause the intestine to extract more of the calcium from our foods. But today our diets are relatively low in calcium, which means that the PTH arm of the control system is usually more active than the calcitonin arm. The concentration of PTH circulating in our blood stream is, thus, a reflection of how close our serum calcium level is to the set point, or how hard the body has to work to keep it there. When calcium intakes are low (either because the food contains little calcium or because, with vitamin D deficiency, we're not absorbing efficiently), PTH levels will typically be elevated. And, accordingly, when absorbed calcium intakes rise, PTH levels fall, until they reach some minimum value below which they drop no further, no matter how much additional calcium we may consume. Other things being equal, a low PTH level is an indication of calcium adequacy. One can see immediately how this approach could be used to define the "normal" calcium intake, i.e., the intake that ensures that the body is not required to adapt or compensate for what the diet has failed to provide.

This is not to suggest that adaptation or compensation are not, themselves, "normal". Indeed they are. Even under optimal ancestral conditions, when human physiology was evolving, external conditions and food sources were constantly in a state of flux. Indeed, the ability to respond, to adapt, and to compensate is an integral feature of life itself and is to be found in all living organisms, from the most simple to the most complex. Even with a theoretically optimal calcium intake, there will be times during the day when some degree of compensation is necessary, simply because there will be times during the day when there is no calcium-containing food within the portions of the intestine that absorb calcium. So we have to be able to adapt. The question is: *How much adaptation is just right?* And: *How much is too much?*

The adrenal hormones are clearly of vital importance in helping us adapt to stressful situations, but nearly everyone knows that living with a high adrenaline level all the time, or a high cortisol level, is neither healthful nor pleasant. Is there a physiological cost from too much PTH, just as there is a cost from too much adrenaline or cortisol? The answer is clearly "yes". Constantly high levels of PTH increase the rate of bone remodeling activity and decrease bone strength in the areas being remodeled. That leads to skeletal fragility and fractures. That is probably the main reason why low calcium intakes predispose to osteoporosis.

The foregoing discussion has focused on calcium intake, properly considered, but it applies, also, to the issue of vitamin D adequacy. The reason, as hinted above, is that the intestine's

ability to increase calcium absorption in response to PTH is dependent upon vitamin D status. One simply cannot absorb enough calcium from typical diets, no matter how high the PTH level, if there is appreciable vitamin D inadequacy. So, a low level of PTH in the blood is an indication not only of the adequacy of diet calcium, but of vitamin D status, as well.



How would one apply this understanding to the requirement for vitamin D? The approach I'm suggesting is to evaluate the relationship between PTH concentration and vitamin D status, as in this figure.

The data behind the figure come from a group of over 2,300 individuals studied in our laboratories at Creighton University in whom measurements were made of both PTH and vitamin D status [serum 25-hydroxyvitamin D – 25(OH)D]. The figure shows clearly the expected high levels of PTH at low vitamin D status values, with PTH concentration falling and becoming essentially flat as vitamin D status rises to levels in the range of 125 nmol/L (50 ng/mL). Exactly the same relationship is exhibited in a report from the National Health and Nutrition Examination Survey, involving a population-based sample of over 14,000 individuals. Both data sets found almost exactly the same vitamin D status level, above which PTH fell no further.

Because there are many factors that influence PTH concentration beyond vitamin D status, this approach will not work very well in determining *individual* requirements of calcium or vitamin D. However, it does work at a *population* level, as the graph shows. The point at which further increases in vitamin D status produce no further decreases in PTH concentration [i.e., a plot of PTH on 25(OH)D is flat] defines the PTH set point for both calcium and vitamin D. This is the point around which the body can exercise its regulatory control of serum calcium concentration with optimal capacity in both directions. The need to compensate, and the duration of adaptation are minimized. Such a value would seem to be a reasonable estimate of optimal vitamin D status, and therefore an indicator of the vitamin D requirement.

Postscript. Another nutrient for which this approach seems preeminently well suited is sodium. Details will have to wait for another post, but it is enough to say here that low sodium diets require a constant adaptative response, without which blood pressure would drop to

dangerously low levels. Sodium intakes requiring the "least adaptation" appear to fall between 2500 and 4500 mg per day.

Posted in Calcium, Nutrient intake requirements, Nutrition, Vitamin D | Tagged calcitonin, hormones, parathyroid, what is normal | 2 Comments

PART ONE: Defining normal – lessons from our ancestors

Posted on April 1, 2013 by Robert P. Heaney
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Part Two: Defining normal – thermostats, feedback and adaptation
Part Three: Defining normal – living on the plateau
Part Four: Defining normal – origins and resiliency

Nutrition doesn't know what normal is.

You might think that the idea of "normal" would be pretty straightforward. We say an engine is running normally if it is doing what it was designed to do, it does so without various kinds of hiccoughs, and it doesn't break down prematurely. In theory the same concept should apply to nutrition, where "normal" would mean getting enough of all nutrients to allow our various organs and systems to run the way they were designed and to continue to run smoothly for as long as possible.

Unfortunately, while we know what a mechanical device is designed to do, we don't have the same assurance when it comes to our physiology. We don't have an owner's manual to consult. Instead, we try to find individuals in the population who appear to be healthy, assess how much of various nutrients they ingest, and consider such intakes to be adequate (i.e.,"normal"). After all, they're "healthy". That seems sensible on the surface, but it is inherently circular because it begs the question of "normal". While such individuals may not be exhibiting recognized signs of nutritional deficiency, that certainly does not mean that current intakes are optimal for long-term physiological maintenance. (A parallel is the regular changing of the oil in our cars which has no immediately apparent effect, but certainly has consequences for the future of the engine). If, as seems increasingly likely, there is a causal role played by inadequate nutrient intake in the chronic degenerative diseases of aging, then we need to find a better way to assess what is "normal".

It's important to understand that "normal" in this sense does not mean that a person with an adequate intake thereby has "optimal" health. Nutrition is terribly important, but it is certainly not the only determinant of health. By contrast, an "adequate" (or normal) nutrient intake is the intake above which further increases produce no further benefit to the individual – long-term or short-term. That's conceptually straightforward, but hard to establish empirically. Of the many difficulties I might list are:

1. The harmful effects of an inadequate intake may not be apparent until later in life; as a result the requisite studies are generally unfeasible;
2. We may not know what effects to look for even if we could mount such a study, and;
3. The required evidence can come only from studies in which one group would be forced to have an inadequate (i.e., harmful) intake, which is usually ethically unacceptable.

Not being able to confront these difficulties head-on, we fall back to presuming that prevailing intakes are adequate and we shift the burden of proof to anyone who says that more would be better. ("Better" here means, among other things, a smaller burden of various diseases later in life, an outcome which, as just noted, may not be easily demonstrable.)

Fortunately there are alternative approaches that could be used and that have clear parallels in other fields of medical physiology. This post is the first of a series in which I address these alternatives, beginning with ancestral intake.

Lessons from our ancestors

It's important to recognize two key points when it comes to ancestral intake.

1. Nutrients are substances provided by the environment which the organism needs for physiological functioning and which it cannot make for itself; and
2. The physiology of all living organisms is fine-tuned to what the environment provides. This latter point is just one aspect of why climate change, for example, can be disastrous for ecosystems since, with change, the nutrients provided by the environment may no longer be adequate.

Thus, knowing the ancestral intake of human nutrients provides valuable insight into how much we once needed in order to develop as a species.

It's helpful to recall that humans evolved in equatorial East Africa and during early years there (as well as during our spread across the globe) we followed a hunter-gatherer lifestyle. During those millennia populations that found themselves in ecologic niches that did not provide what their bodies actually needed, simply didn't survive. The ones that did survive – our ancestors – were the ones whose needs were matched to what the environment provided. The principles of Darwinian selection apply explicitly to this fine-tuning of nutrient intakes with physiological functioning.

Thus knowing how much protein or calcium or vitamin D or folate our pre-agricultural ancestors obtained from their environments gives us a good idea of how much might be optimal today. There is no proof, of course, that an early intake is the same as a contemporary requirement, because many other things besides diet have changed in the past 10,000 years. But since we have to presume that *some* intake is adequate, it makes more sense to start, not with what we happen to get today, but with the intake we can be sure was once optimal. The burden of proof should then fall on those who say that less is safe, not on those who contend that the ancestral is better than the contemporary intake.

How do we know what the ancestral intake of many nutrients might have been? Certainly, in some cases, we don't know, and this approach, therefore, might not be possible for such nutrients. But, surprisingly, we do have a pretty good idea about the primitive intake of many nutrients. And when we have the data, why not use what we do know for those nutrients?

There are not very many populations today living in what we might call the ancestral lifestyle, and often they are in marginal habitats which may not be representative of what early humans experienced. But that has not always been the case. Over the last 150 years there has been extensive, world-wide, ethnographic study of native populations with particular emphasis on those who have come into stable equilibrium with their environments. There are reams of data with respect to dietary intakes reposing in various libraries and museums, remarkably

comprehensive, and shedding priceless light on the habits and status of people we can no longer know or experience first-hand.

Take vitamin D as just one example. We know that proto-humans in East Africa were furless, dark-skinned, and exposed most of their body surface to the sun, directly or indirectly, throughout the year. We know how much vitamin D that kind of sun exposure produces in the bodies of contemporary humans, both pale and dark-skinned, and we have made direct measurements of the vitamin D status of East African tribal groups pursuing something close to ancestral lifestyles. We know also that, as humans migrated from East Africa north and east, to regions where sun exposure was not so dominant, and where clothing became necessary for protection from the elements, skin pigmentation was progressively lost, thereby taking better advantage of the decreased intensity of UV-B exposure at temperate latitudes and enhancing the otherwise reduced vitamin D synthesis in the skin.

All of these lines of evidence converge on a conclusion that the ancestral vitamin D status was represented by a serum concentration of 25-hydroxy-vitamin D (the generally agreed indicator of vitamin D nutritional status) in the range of 40–60 ng/mL (100–150 nmol/L). Recent dose response studies show that achieving and maintaining such a level typically requires a daily input, from all sources combined, of 4000–5000 IU vitamin D.

Thus, using this ancestral intake criterion of "normal", one might formulate a contemporary recommendation for vitamin D nutrient input somewhat as follows:

"We don't know for certain how little vitamin D a person can get by on without suffering health consequences, but we do know that our ancestors had an average, effective intake in the range of 4000–5000 IU/day. We also know that this intake is safe today. Thus we judge that the most prudent course for the general population is to ensure an all-source input in the range of 4000–5000 IU/day until such time as it can be definitively established that lower intakes produce the same benefits."

Posted in Calcium, Nutrient intake requirements, Nutrition, Vitamin D | Tagged ancestral intake, what is normal | 2 Comments

Taking Recommendations to Task

Posted on March 19, 2013 by Robert P. Heaney

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Experts disagree with a federal task force's findings on the benefits of calcium and vitamin D supplementation.

Late in February 2013 the U.S. Preventive Services Task Force (USPSTF) issued recommendations that have rained on the parade of those of us concerned with optimizing health with vitamin D supplements and adequate dietary calcium intakes. Or so it would seem, at least from the headlines in the news stories. The recommendations were interpreted to have said that most of us shouldn't take calcium and vitamin D supplements.

That's not accurate.

What the Task Force actually said was that they couldn't find enough evidence to evaluate the balance of possible risks and possible benefits from vitamin D supplements when taken to prevent fractures in the fragile elderly. Accordingly, they could make no recommendation. Most experts actively working with vitamin D disagree with that statement. There *is*, in fact, an abundance of evidence that vitamin D supplementation does help prevent factures.

But whether or not such evidence exists, it's important to note a curious feature of the Task Force report. They had previously recommended vitamin D supplementation for the prevention of falls in older adults, and they restated that recommendation in this most recent release. In a sense, therefore, the new recommendation on fractures is moot, because individuals already taking the vitamin D needed for the prevention of falls will automatically get whatever fracture benefit may be associated. In virtually so many words the Task Force said: "We can't recommend supplements for fracture prevention, but we do recommend them for reducing risk of falls." Both statements apply to the same group of individuals – fallers who thereby fracture.

How can it be that the Task Force finds the evidence inconclusive, while vitamin D experts find it persuasive? The most likely reason is that the Task Force relied in part on what are called systematic reviews, which attempt to pull together all the "relevant" literature. The problem is that systematic reviews are compiled by individuals expert in clinical trial execution, but not, unfortunately, expert in vitamin D biology. So they don't automatically know which studies are relevant and which are not.

That's clear from the fact that the reviews on which the USPSTF relied actually included several large studies that were not adequately designed to evaluate whether vitamin D might reduce fracture risk. Not being expert in vitamin D biology, the reviewers didn't know that. The USPSTF itself has no members who were expert in vitamin D, so they, too, didn't recognize the problem created by including such studies in the reviews they relied on. In point of fact, if the reviews had been confined to properly designed studies, the evidence would have been crystal clear: vitamin D and calcium do reduce fracture risk in the elderly. And they do so safely.

Unfortunately, as just noted, none of the 17 members of the Task Force is an expert in vitamin D biology. Perhaps therefore they can be excused for not knowing that the levels of vitamin D commonly being used today barely reproduce what our grandparents got from their greater time outdoors. And even that is well below what would have been the vitamin D intake of early humans living in East Africa, where sunshine produced vitamin D year round. One should have thought that the proper approach would have been to recommend supplementation to the level of the ancestral intake and to shift the burden of proof to those who say that lower intakes are safe. But that's not the approach the Task Force took.

It's helpful also to remember that the Task Force is a very conservative group – by intention – and is mostly concerned not with nutrients, but with medical interventions, particularly diagnostic tests such as mammograms, colonoscopies, and prostate cancer screening. It's relatively straightforward to evaluate the effectiveness of such medical tests. You look at the totality of outcomes in individuals who have had the tests and compare them with those who haven't (the control group). With mammograms or prostate cancer screenings, for example, there is not only the benefit of early detection, but the downside risk of radiation and surgical damage, affecting everybody, even those who didn't have a cancer and therefore would not have benefitted (but might have been harmed).

But with nutrients like vitamin D, it's another question entirely, since there is no true control group. Everybody gets some of every nutrient, and the question is not whether a particular nutrient is efficacious, but how much must we have to ensure optimal health. The kind of evidence the Task Force applies, for example, to screening for disease is not well-suited to answer such a question.

Another note of caution. The Task Force approach presumes that we're all the same. A study that failed to find an *average* effect greater than one would expect from random chance alone, is deemed "negative". But the groups of people studied may well have contained, for example, subgroups of individuals who responded strongly to the intervention, while the majority didn't respond at all. The Task Force doesn't look at whether it works in *some* individuals. Instead its focus is what may be the balance of risks and benefits for the *whole* U.S. population.

Fortunately downside risk is not much of an issue with nutrients. So, if only one-fourth of the population benefits from extra vitamin D (but we don't know which fourth that is), the real question is does the extra vitamin D hurt the other three-fourths who may get no additional benefit? The answer is "No". The safety profile of vitamin D is actually very good, so long as one does not exceed the tolerable upper intake level promulgated recently by the Endocrine Society of the United States (10,000 IU/d).

Should we all stop taking vitamin D? My family and I don't plan to.

Change Your Oil, Ma'am?

Posted on February 4, 2013 by Robert P. Heaney
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Most of us know that we're supposed to change the oil in our cars regularly, and most of us, I think, do a pretty good job of seeing to such preventive maintenance. But what happens if we don't? The car still runs today pretty much as it did yesterday, and it will tomorrow, as well. We cannot easily tell, from the performance, that changing the oil regularly makes much of a difference. But we know from experience that sooner or later the engine breaks down or loses power.

Nutrition is just like that. If we have a poor diet today, or this week, we still function pretty much as before. But slowly, imperceptibly, our body systems begin to break down. Our reserves diminish. That breakdown is called, in medicine, "chronic disease" – hypertension, arthritis, osteoporosis, diabetes, heart disease, cancer, and the like. All such system breakdowns have multiple causes, and poor nutrition is only one of many. But it is one that is within our individual ability to influence. We cannot control our genes, and we cannot easily control our environments, but we can control what we eat.

Available evidence indicates that optimal nutrition can reduce our risk of prematurely succumbing to one of those system failures by as much as 50% or more. Nutrition is one of the most powerful – and most economical – tools to maintain vigorous good health throughout life. It is not a guarantee – other harmful influences are at work. But, like wearing seat belts, it very significantly reduces our risk.

The Institute of Medicine lists about 20 nutrients that are considered essential, and for which it has specified a daily requirement. There are probably another 20 or so, also necessary, for which the requirement is uncertain. Very briefly, good nutrition consists of eating a diet that provides all those essential nutrients. There are two main reasons why that is harder to do today than might have been the case in, say, the 1950s. First, we are much less physically active today than we were then, so we cannot afford to eat as much. And second, the foods readily available to us are calorie-dense and often nutrient-poor. So, for many nutrients, we hit our daily calorie limit well before we get as much calcium or folate or B_{12} or many of the other nutrients we need. Exercise – actually, physical work – is important for another reason, as well. Many of our body systems, such as our bones, were designed for mechanical work and without it, they can never come up to their designer's specifications for strength. Nutrition, while essential, is not sufficient by itself.

Unfortunately, physicians are rarely good sources of nutrition information and advice. They receive almost no nutrition training in school and in practice their time is consumed with fixing what is broken. Nor do they, in today's fragmented urban environment, have the opportunity to undertake the efforts at disease prevention that we all recognize as the most sensible approach. Pediatricians and obstetricians are the sole exceptions to that statement. For both, the short time horizons and the continuity of contact allow effective preventive efforts. But it pretty much stops there.

Unfortunately, also, much of medicine's emphasis is negative: "Cut your salt intake"; "cut saturated fats"; "ban transfats entirely"; "watch your cholesterol" . . . I say "unfortunately" for two reasons. First, a negative approach is the wrong way to go about something as positive as eating well. And second, the evidence for those prohibitions is not only lacking, but in

recent years studies have shown that they are often flat out wrong. There are transfats in milk, for example, that are essential for health. Eliminating them from our diets would be harmful rather than helpful.

Or, if you are found to have high blood pressure, your doctor will almost certainly urge you to cut back on your salt intake. Why? Because doing so will lower your blood pressure slightly, and because high salt intakes cause hypertension in a certain strain of rats. But this negative strategy ignores two key points:

1. Increasing your calcium intake will lower blood pressure more than will reducing salt; and
2. In order for salt to produce high blood pressure in those rats, investigators had to first put the animals on low calcium intakes. The positive approach simply outperforms the negative almost every time.

Nutrition is still a young science, and we are a long way from knowing all that we need to know. Still, the positive approach seems the best strategy. Worry less about avoiding certain nutrients and concentrate instead on eating foods that will give you what your body needs for the long haul.

What are some of those foods?

1. ***Dairy***, for starters. Dairy products are just about the most nutrient-dense foods we can eat. When calories count, as they do for most of us, dairy delivers excellent nutrition without excess calories. Reduced fat milk can be an even better energy bargain, but do not focus exclusively on skim; we need some of the essential fats in milk.
2. Second, lots of ***fruits and vegetables***. (Do not fret over "fresh". Modern food production methods get broccoli from field to freezer in less than 24 hours, locking in its full complement of nutrients – while the broccoli in the food produce aisle was days old before it got there, and older still when we consume it – with its nutritional value deteriorating all the while.)
3. Next is ***meat***. Yes, meat. Human physiology is an omnivore physiology, that is, it is optimized to consume a mix of animal and plant foods. In fact, several of the nutrients recognized as essential for humans can be found only in animal foods, and for others, only animal foods provide the nutrient in adequate quantity.
4. Finally, ***supplements***. What is their role? It should be what their name indicates. They should *supplement* an otherwise good diet, not substitute for it. Calcium is a good example. Calcium has many positive effects in addition to its recognized role in bone health. But those effects are best realized when calcium comes in as a part of the dairy package. That is not because it is better absorbed or utilized from dairy, but because dairy-poor diets have repeatedly been shown to be deficient in several other essential nutrients in addition to calcium. For example, even the bony benefits of calcium cannot be fully realized if a person is deficient in vitamin D and/or has a low protein intake.

Nutrition is not just like changing the oil regularly. It's also about working together, as in a symphony orchestra. You need *all* the instruments. Beethoven's 5th would sound pretty strange if played only on the flutes and percussion. Good nutrition is about good eating, and good eating is fun. Enjoy!

Posted in Nutrient intake requirements, Nutrition | Tagged tips | 2 Comments

Calcium: The Real Story

Posted on January 4, 2013 by Robert P. Heaney
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One of the best kept secrets of nutrition is that nearly all body systems need nearly all nutrients. When we don't get enough calcium, for example, it's not just our bones that suffer, but the rest of our body as well.

The connection between calcium and bone health seems obvious, as calcium is what gives bone much of its strength. The amount of bone we have, particularly as we are growing, depends substantially on how much calcium we consume. But once we have amassed an adult skeleton, calcium still works to make bones strong, though in a surprising way. The body maintains blood calcium levels very tightly by making three adjustments, as needed:

1. The amount of calcium we absorb from food
2. The amount of calcium we excrete through the kidneys
3. The amount of calcium we draw out of our bone reserves.

The third adjustment, the withdrawal of calcium from bone, is accomplished not by leaching calcium out, but by tearing down small volumes of bone and scavenging their calcium. This activity, known as bone remodeling, is just like the remodeling of a building, i.e., we tear out old structures and replace them with new. When calcium intake isn't sufficient to meet the body's needs, the rate of remodeling speeds up, so as to release more of the bone's calcium. With bone, just as with our buildings, a structure being remodeled is fragile until the repair has been completed. Not surprisingly, therefore, a skeleton undergoing a lot of remodeling is much more fragile than a skeleton with less.

Calcium affects the rate of bone remodeling directly and immediately. If my intake of calcium is low today, the body doesn't wait until tomorrow or next week to do something about it. It increases bone remodeling *today*, so as to access the calcium it needs *today*. And similarly, if I have been remodeling a lot of bone every day because my calcium intake is low, then *today*, when I get calcium intake back up to where it ought to be, remodeling immediately slows down. That's the reason why, in so many of the studies showing an anti-fracture benefit of calcium, the effect begins immediately. One doesn't have to wait to build up the skeletal mass (which changes at a rate of only a few percent per year).

What about other body systems?

Kidney Stones
One example may seem surprising. A high calcium intake lowers the risk of kidney stones. It might be natural to think: "Well, since I have had a kidney stone, I should reduce my calcium intake." Actually, that's the exact opposite of what you should do. Lowering calcium intake *increases* your risk of stones. The reason is that the commonest form of kidney stones consists not only of calcium, but of a substance called oxalate. Oxalate is a much more potent risk factor for stones than is calcium itself (even though calcium is a component of the stone). The oxalate in our urine comes both from internal metabolism and from our diet. When calcium combines with oxalate it becomes insoluble, and precipitates out of solution. If that occurs in the kidney, it can lead to stone formation, but if that complex occurs in the gut itself, where ingested yet unabsorbed calcium interacts with food oxalate, then that oxalate never gets into

the body at all. So by increasing calcium intake, the oxalate doesn't have to be excreted through the kidneys, and doesn't contribute to stone risk.

Colon Cancer
There is yet another beneficial action of calcium within the intestinal cavity. Unabsorbed dietary calcium binds not only with oxalate, but with unabsorbed fat and bile acids as well. Both are irritants and tend to promote colon cancer. But, by binding them, calcium neutralizes these irritants and thus lowers the risk of adenoma recurrence or cancer development.

Hypertension and Weight Loss
And it doesn't stop there. Calcium also helps in control of blood pressure, maintenance of body composition, and numerous other activities that sustain optimal health. For that reason, a high calcium intake should be part of the treatment regimen for patients with hypertension. It won't always restore normal blood pressure by itself, but it definitely enhances the effect of blood pressure medications. So, too, if you're on a weight loss diet, a high calcium intake helps – both to take pounds off and to keep them off.

There's even more, but that's another story.

Posted in Calcium, Nutrition | Tagged bone health, calcium, colon cancer, hypertension, kidney stones, weight loss | 3 Comments

What is Lactose Intolerance?

Posted on January 4, 2013 by Robert P. Heaney
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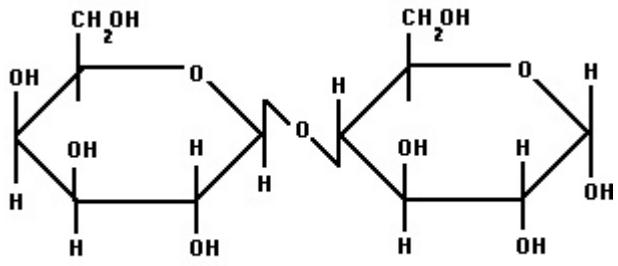
"… I know I should drink more milk, but I can't. I am lactose intolerant …"



Galactose ——— Glucose

Lactose is the name given to the sugar that is contained in milk. It's what biochemists call a disaccharide, which means it is a complex of two simple sugar molecules, glucose and galactose. It's the principal carbohydrate in the milk of all mammals. It's an important source of energy during growth, but to be utilized by the body, it first must be split into its component sugars. This is accomplished by an enzyme that is a part of the digestive juices of infants, called **lactase**. [There is a hint here for you cross-word puzzlers. The technical names for sugars usually end in *–ose*, while the technical names for enzymes, usually end in *–ase*.]

Lactose is not found in foods other than dairy and, under ancestral conditions, after weaning, lactose typically disappeared from the diet, human as well as lower animal. The body, in its wonderful economy, reduces its production of lactase as we grow older, starting sometime after weaning. Under ancestral conditions, lactase simply wasn't going to be needed again. That gradual loss of lactase activity occurs to a greater extent in individuals of East Asian or

African extraction than in those of European ancestry, but we all lose some as we grow older. The problem is that about 10,000 years ago humans began to domesticate milk-producing animals, and thus dairy products entered the post-weaning diet. Our intestines, programmed as they had been over the millions of years of primate evolution, have had very little chance to catch up with this relatively very late addition to the adult human diet.

In the technical lingo of the field, the relative absence of lactase in the digestive systems of many adults is called "**lactase nonpersistence**", and the fact that milk sugar cannot be easily digested by such individuals is termed "**lactose maldigestion**". In individuals who are lactose maldigesters, lactose, instead of being split and absorbed, moves into the distal bowel. The bacteria that normally reside there then digest the sugar for their own use, producing hydrogen gas in the process. Sometimes that hydrogen gas produces abdominal symptoms such as bloating, flatulence, cramps, or diarrhea. It's that condition, induced by the unaccustomed consumption of milk, that is called "**lactose intolerance**".

But not all lactose maldigesters have symptoms. In fact, most do not. Studies of national population samples, consisting of people of different racial backgrounds, have shown that only about 14% of the adult population has any symptoms at all that could be related to lactose ingestion, even though the prevalence of lactose maldigestion must have been 3–5 times higher than the number with symptoms.

It's important to understand that lactose is not found in all dairy products, but mainly in milk and milk products, and not in products such as cheese. That's partly because the molds making the cheese utilize the lactose as a source of energy, and partly because lactase, being water soluble, is carried off in the whey. Moreover, live culture yogurts, which do contain lactose, also contain organisms that break it down for us, and hence neither hard cheeses nor live culture yogurts are likely to evoke the symptoms of lactose intolerance. It's also important to understand that the symptoms of lactose intolerance are dependent upon how much lactose we ingest. The amount of lactose in one-half serving of milk (4 ounces) has never been shown to cause symptoms, even in those who complain of serious lactose intolerance. That fact provides a hint as to how we can deal with the problem in those who would like to be able to drink milk and yet do have symptoms.

But, before launching into treatment, it's useful also to understand the relationship that exists between us as human beings and the many billions of micro-organisms that live with us in our bodies, many of them in our intestinal tracts. Those of us of an older generation were taught to fear germs. They were bad … or dirty … or caused disease … or all of the above. Manufacturers have made millions of dollars by selling us products such as antiseptics and disinfectants. Some germs are, indeed, harmful, but most are friendly, most of the time.

One of the friendly things these bacteria do is to help us digest complex compounds in our food that our intestines aren't equipped to handle. One good example are the foods that we recognize as gas-forming, such as beans and the cruciferous vegetables (broccoli, cauliflower, brussel sprouts, etc.) – and, in the case of the subject of this article, milk. The bacteria in our intestines are capable of producing the enzymes needed to digest these foods. But our intestinal organisms are thrifty. They won't produce the needed enzymes unless we consume the foods containing these compounds regularly. What, after all, would be the point of an organism making a metabolic expenditure to produce enzymes that it wasn't going to use? As it turns out, our intestinal organisms are quite capable of producing lactase for us, but only so long as we provide them with a diet that contains milk on a regular basis.

As a result someone who complains of severe lactose intolerance symptoms can almost always be brought up to the point of consuming three full glasses of milk per day without symptoms if they build up the exposure gradually, slowly getting the bacteria in our intestines used to such a diet. The program usually goes something like this: add a half a glass of milk with a main meal on day 1, then a half a glass to two meals on day 2, and so forth until one builds up to three full servings per day. And here's the important point: you have to keep drinking that milk, or the bacteria will stop producing the enzyme needed to digest it for you. So, obviously, this strategy only works for people who want to be regular milk drinkers.

What can we do for individuals who want to be able to drink milk, but only occasionally? They may well experience symptoms (even though, as we have seen, most maldigesters never actually do). There are two options available. One is to use lactose-reduced or lactose-free milk, generally available in most grocery stores and the other is to take a small tablet containing lactase at the time one drinks the milk. These tablets are also generally available over the counter in drug or grocery stores.

Getting enough calcium is important, and getting it in conjunction with the many nutrients that are contained in milk is even better than getting it in supplement form. One thing is clear: lifelong milk avoiders – for whatever reason – run an increased risk of suffering osteoporotic fractures. So if lactose intolerance appears to be a barrier to you, then it is helpful to know that you can train your body (and its friendly bacteria) to digest the lactose for you. Or, you can get the needed calcium and other nutrients from alternative dairy products, such as hard cheese or live culture yogurts. Either way, don't let lactose intolerance get between you and your getting enough of the nutrients you need for bone health.

Calcium Scare a False Alarm

Posted on December 12, 2012 by Robert P. Heaney
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"I just don't know what to do about my calcium …"

This complaint has been heard thousands of times across North America these past two years, as women have turned to their illness-care providers for advice about protecting themselves from osteoporosis. The problem started with extensive media coverage of a study published in the British Medical Journal, stating that calcium supplement use was associated with a slightly increased risk of heart attack. Many stopped taking their calcium supplements entirely, and physicians, blindsided by the report, immediately became more cautious in recommending use of calcium supplements.

The problem was clearly a serious one, as recommended calcium intakes for Canada and the United States range from 1000 to 1500 mg per day, with food typically providing only about half that amount. At least three separate Consensus Development Conference Reports,

published by the National Institutes of Health in the U.S., had recommended calcium supplement use, both for total nutrition and specifically to reduce risk of osteoporosis.

Osteoporosis experts were quick to respond, pointing out serious flaws in the methods used by the investigators of the studies concerned. Unfortunately their refutation, though published in the medical literature, elicited little or no media coverage. So the confusion persisted and calcium supplement use has dropped by perhaps as much as 14% over the past two years. This has undoubtedly led to an increase in otherwise preventable osteoporotic fractures.

Finally, this fall, three definitive publications are appearing in major nutrition and osteoporosis journals, concluding that the calcium supplement scare was a false alarm – that there is no increased risk of coronary disease in individuals taking recommended amounts of calcium supplements. Among other approaches, the authors of these "all clear" publications reanalyzed the many papers published on this topic and simply found no significant evidence of a connection between calcium supplements and heart attacks.

In 2004 the U.S. Surgeon General, in his report on bone health and osteoporosis noted that "Calcium has been singled out as a major public health concern because it is critically important for bone health and the average American consumes levels of calcium that are far below the amount recommended …" As all the official statements on this topic stress, the best way to get the calcium we need is from food (because foods contain the many other nutrients needed for calcium to produce its full benefit). What we can't or won't get from food, we should get from supplements. That's still true today, especially with the new reassurance that calcium supplements are safe.