It's a U-Shaped World:
A Batesonian Prescription for Promoting Public Health

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I am a cancer researcher and what's on my mind today is this thorny question: Why is it so difficult to find "good things" that promote health? Perhaps the difficulty reflects the dramatic contrast between the simple questions we ask such as, "Why do we age?", and the complexity of the underlying biology. Perhaps we could blame it on culture. I wonder if Gregory Bateson would blame it on, for example, the Desperate Housewives – those home wreckers with their dirty laundry. Actually, I'm not sure Bateson would have paid any mind whatsoever to that television show. He did, however, devote ample attention to *homeostasis wreckers*. Bateson spent considerable time considering the things that could wreck a biological system. He called them "design disasters in biological systems."[1] In this paper, I'd like to focus your attention on one of those design disasters.

Thirty years ago in *Mind and Nature*, Bateson wrote, "There are no monotone values in biology".[2] Bateson explained further: "Desired substances, things, patterns, or sequences of experiences that are in some sense "good" for the organism … are never such that more of the something is always better than less of the something. Rather, for all objects and experiences, there is a quantity that has optimum value."[2] I contend that one of the real villains in public health today is the overly simplistic view of health promotion held by the public, which ignores Bateson's wisdom. This attitude is captured in the expression "Just show me the good things and I'll grab as much of them as I can." I hope to convince you that Bateson's thinking was right on target – that when it comes to your risk of disease and how much "good things" you should have, it's a U-shaped world (Figure 1). You don't want to have too little or too much of "good things".

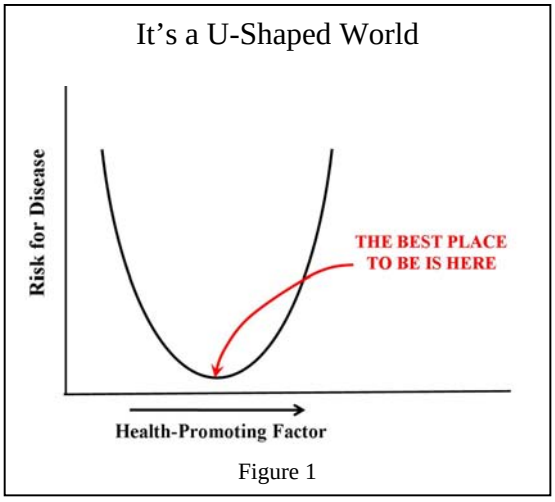

Figure 1

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Further, I contend that scientists and media often co-conspire in this public health confusion. This culminates in research results that are frequently reported to the public out-of-context. In the cartoon in Figure 2, a guy is sitting behind the wheel of his car, which bears a license plate that reads "I'm Sexy". The traffic officer who pulled him over says to the guy: "I'm writing you two tickets, $100 for speeding and $250 for misleading the public." Regretfully, no one is pulling over scientists or the media to "ticket" them for misleading the public. My goal is to impress upon you that health promotion is a general semantics concern (Figure 3). Today, I ask you to consider the critical role that general semantics could play in mediating the 3-ring circus between scientists, media, and the public.

Misleading the Public

Figure 2

Health Promotion:
A General Semantics Concern

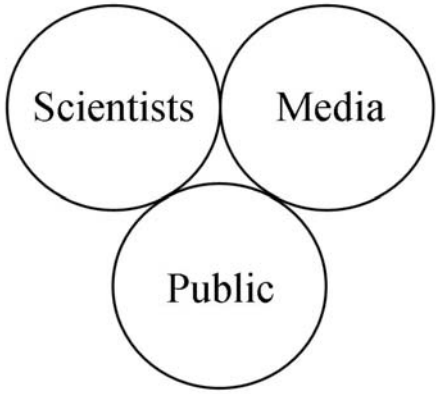

Figure 3

My story today is a dirty story about prostate cancer prevention. It centers around the question: Can men significantly reduce their risk of prostate cancer by taking dietary supplements? I call it a dirty story because it's about selenium, and selenium comes from the soil. What is selenium? Selenium is an essential trace nutrient found in many of the foods we eat. Selenium is part of our antioxidant defenses, protecting against the oxidative stress that our bodies produce each day. More than 400 animal studies celebrate the anti-cancer activity of selenium. Not surprisingly then, in 2001 the National Cancer Institute launched the largest-ever prostate cancer prevention trial called SELECT. More than 32,000 men enrolled in the SELECT study were randomized to receive selenium, vitamin E (another antioxidant nutrient) or both, with prostate cancer incidence as the study end-point. The prospect that a man's risk for contracting prostate cancer could be reduced by taking a little pill was really exciting.

But as the SELECT study began, there were still two very basic questions that remained unanswered about selenium and cancer prevention: (1) What is its anti-cancer mechanism? and (2) What is the most effective dose? We will focus today on the second question. Our research group saw this as a great opportunity, because we were experts on the prostate cancers of dogs. Dogs and humans are the only two species that naturally develop prostate cancer[3]. And we were the research bunch that had the best shot at putting dogs to work to get to the bottom of this dose issue.

We began focusing our efforts on determining what is the best dose of selenium for prostate cancer prevention. When researchers seek to establish the optimal dose of an intervention, whether it be a dietary supplement or other lifestyle choice such as exercise, we generate what are called dose-response curves. If more of your factor is better, then you get a dose-response curve that looks like Figure 4. But a scientist named Mertz more than 25 years ago[4] put forth a model predicting that the biological response between any essential nutrient and biological process is not linear, but instead U-shaped (Figure 5). He had little data, just a strong hunch.

Finding the Optimal Dose

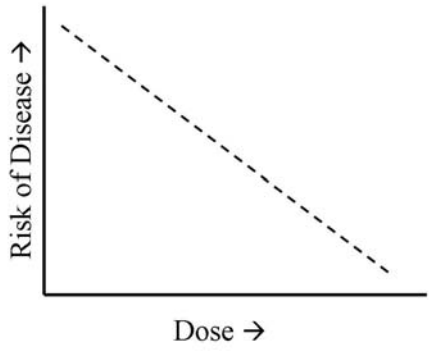

Figure 4

Theoretical Relationship Between Cancer Risk and Concentration of a Cancer-fighting Nutrient

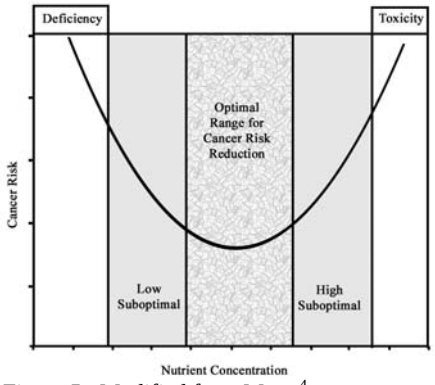

Figure 5: Modified from Mertz[4] Used by Permission

So, we set out to probe the relationship between selenium status and genetic damage within the prostate. To accomplish this, we conducted a randomized feeding trial in 49 elderly, sexually intact male beagle dogs that were physiologically equivalent to 65 year-old men. We determined the selenium status of the dogs by measuring how much selenium was in their toenails and we calculated the amount of DNA damage in the prostate using a laboratory test called alkaline Comet assay. Figure 6 shows what we found. The relationship between selenium status and prostatic DNA damage was indeed U-shaped, thus presenting the first data that, at least for selenium and a cancer-associated process in the prostate, Mertz was right.

Relationship Between Selenium Status and Prostatic DNA Damage in 49 Elderly Dogs Physiologically Equivalent to 65-Year Old Men

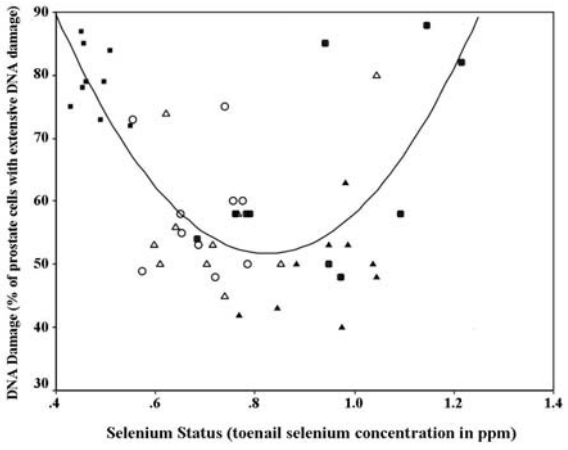

Figure 6: Waters et al.[5] Used by Permission

Even though we published our results in a top-flight cancer research journal in 2005[5], you might be a tad skeptical of our findings and ask: Are the results of these animal studies relevant to the relationship between selenium status and *human prostate cancer risk*? The skepticism is justifiable – we studied dogs, not men; our end-point was prostatic DNA damage, not cancer. It is beyond the scope of this paper to show you the data, but data from human studies of selenium and prostate cancer risk remarkably parallel the U-shaped dog curve[5, 6]. The take-home message: when it comes to selenium and cancer prevention, more is not necessarily better.

You might wonder if the U-shaped curve is something peculiar to selenium and cancer. The answer is no. Just as Bateson predicted, looking at the world around us, we can find many examples of U-shaped relationships. These include the association between: the risk of death and sleep duration in women[8]; blood sugar levels and whether you survive a heart attack[9]; cholesterol levels and overall mortality – your mortality goes up if your cholesterol is too high *or too low*[10]. Scientists who study longevity in worms know that no heat is associated with a certain lifespan, a little bit of heat stress actually increases longevity, but more heat is detrimental[11]. Even Dali's moustache is U-shaped (Figure 7).

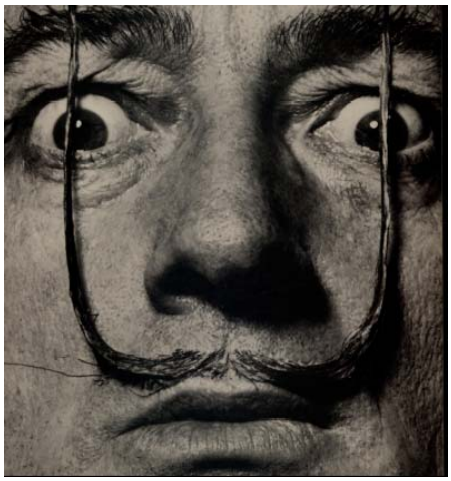

Figure 7 ©Philippe Halsman Used by permission

Returning to the health benefits of selenium, let's look at what the public is hearing about selenium. In a press release dated July 10, 2007, MSNBC.com ran this headline: "Supplement Linked to Diabetes in Study: 200 Micrograms of Selenium Daily Raised Risk by 50%, Researchers Say". This news story was referring to a scientific paper that was published that summer in *Annals of Internal Medicine*[12]. The results of that study are shown in Figure 8. The solid line shows that the incidence of newly diagnosed cases of diabetes rose more sharply in men treated with selenium compared to placebo controls (dotted line). But, perhaps we should look at the data in another way – in a way that Bateson would likely say is a more meaningful way of thinking. Let's divide the men into three separate groups based on their selenium levels *prior to receiving selenium supplementation*. When we do this (Figure 9)**,** neither the men with the lowest selenium prior to supplementation nor those with medium levels prior to supplementation had an increased risk for developing diabetes from the additional selenium they received. It was only those men who had the *highest levels of selenium prior to supplementation* that experienced an increased risk for diabetes – a risk that increased by almost 3-fold. Is that the message the public heard about selenium? Not even close.

Cumulative Incidence of Type 2 Diabetes Mellitus

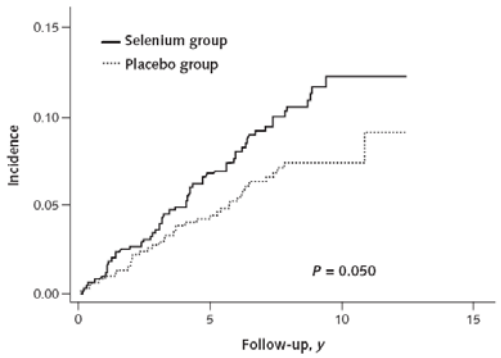

Figure 8: Stranges et al.[12] © Ann Intern Med
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Influence of Baseline Selenium Status
on Incidence of Type 2 Diabetes Mellitus

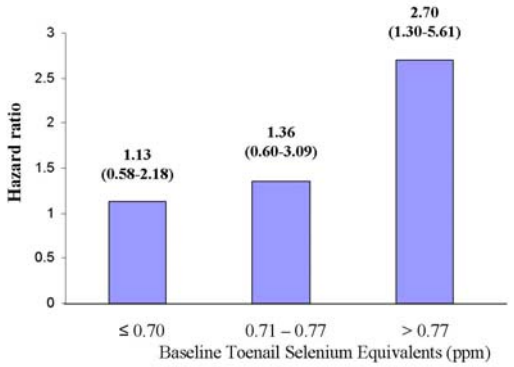

Figure 9: Data from Stranges et al.[12]

Now, let's fast forward to January 2009. The press release read: "Vitamins Can't Fight Big Killers – Supplements of No Use in Prevention of Heart Disease or Cancer". Another press release informed: "Prostate Cancer Prevention Study Halted – SELECT Findings Dash Hopes Raised by Earlier Studies." These press releases signaled the early stoppage of the SELECT study. An interim analysis of the results showed that selenium supplementation was not protecting men against prostate cancer. This lack of benefit was seen amidst a troubling trend toward increased type 2 diabetes in the men receiving selenium. These preliminary scientific findings were published in the *Journal of the American Medical Association* in January 2009[13].

I have a concern here. When it comes to interpreting the results of the SELECT study, is there a chance we are just lost? If you are in a shopping mall and you are lost, you look for the map that tells you "You Are Here". Likewise, if you are visiting the battlefield at Gettysburg where Lincoln delivered his famous address, you look for the map that says "You Are Here". So let's look at two maps of our own (Figures 10 and 11) and see if they can assist us. If you were the average guy in the SELECT study <u>before</u> selenium supplementation, the map indicates that you were already in the optimal range (Figure 10). But, if you were the average guy in the SELECT study <u>after</u> selenium supplementation, the map indicates that taking additional selenium catapulted you way up and out of the optimal range (Figure 11). The press release makes the results sound so *unexpected*. But these simple maps tell the real story. Isn't the observation that the guys in the clinical trial did not benefit from additional selenium *more of an expected result* than an unexpected result?

If You are the Average Guy in the SELECT Study
Before Supplementation …

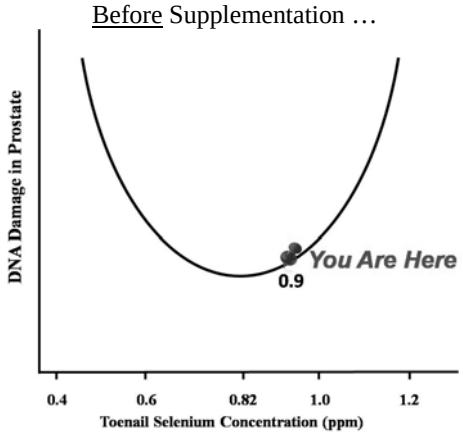

Figure 10

If You are the Average Guy in the SELECT Study
After Supplementation …

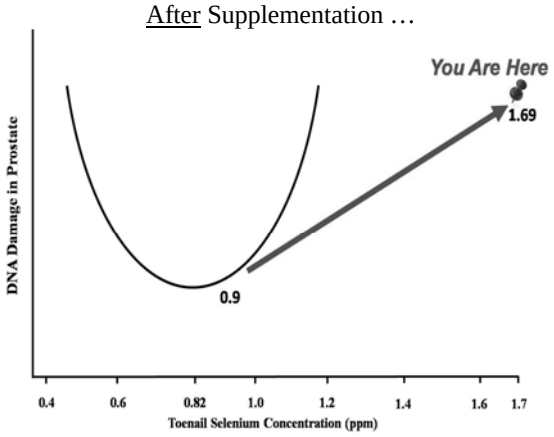

Figure 11

Now for the most troubling part. The following is the statement that appeared in the letter that each of the participants in the SELECT study received in October 2008 from the scientists who ran the clinical trial: "We now know that selenium and vitamin E do not prevent prostate cancer." *Is that what we really know?* I think Gregory Bateson would say that what we know is that there are no monotone values in biology. The goodness of selenium, or anything else for that matter, cannot go up and up and up. The selenium replete men of the SELECT study told us everything they could. The results of a large-scale clinical trial that misses the target cannot be used as evidence to invalidate two decades of careful scientific work about a cancer-fighting nutrient[14]. Can it?

I think Bateson would smell a rat here. He would point out the error of logical type[15]. And he would tell us that errors of logical type can make us feel lost. Instead of asking "Is this thing good or bad for me?" we need to help the public and health professionals to ask the better question: "Under what conditions would I benefit from this thing?"

In conclusion, promoting health in a U-shaped world poses distinctive challenges. The public craves simplified health messages. A general semanticist, like Bateson, would quickly recognize Aristotelian either-or-ness at the root of these oversimplified health messages. The public expects large-scale clinical trials like the SELECT study to provide us with a concrete verdict like: "Selenium is good for you." But, in a U-shaped world where more is not necessarily better, this is a meaningless statement that offers no guidance at all. The public is hearing the results of health research out of context – a problem of paramount importance because context determines meaning. That is why I believe that applying the principles of general semantics could really help us tidy up this health communication mess.

I end with one of my favorite quotes from Gregory Bateson, a quote that I call "Bateson's Rule of 9/10ths". He wrote: "The pre-instructed state of the recipient of every message is a necessary condition for all communication. This book can tell you nothing unless you know 9/10ths of it already." [1] I can only hope that, in the spirit of effective communication across the generations, my message today added seamlessly to the 9/10ths you already knew.

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