Ms. Denise Minger has published a critique of our book, The China Study, as follows.

The China Study: Fact or Fallacy? « Raw Food SOS: Troubleshooting on the Raw Food Diet

It is both interesting and gratifying that there has been such a huge response, both on her blog and on those of others. This is a welcome development because it gives this topic an airing that has long been hidden in the halls and annals of science. It is time that this discussion begin to reach a much larger audience, including both supporters and skeptics.

I hope at some point to be able to read all of the discussions and the questions that have been raised, but present deadlines and long-standing commitments have forced me, for now, to focus on the most common concerns and questions, in order to respond in a timely manner here.

Kudos to Ms. Minger for having the interest, and taking the time, to do considerable analysis, and for describing her findings in readily accessible language. And kudos to her for being clear and admitting, right up front, that she is neither a statistician nor an epidemiologist, but an English major with a love for writing and an interest in nutrition. We need more people with this kind of interest.

I am the first to admit that background and academic credentials are certainly not everything, and many interesting discoveries and contributions have been made by "outsiders" or newcomers in various fields. On the other hand, background, time in the field, and especially peer review, all do give one a kind of perspective and insight that is, in my experience, not attainable in any other way. I will try to make clear in my comments below when this is particularly relevant.

My response can be divided into three parts, mostly addressing her lack of proportionality—what's important and what's not.

- Misunderstanding our book's objectives and my research findings
- Excessive reliance on the use of unadjusted correlations in the China database
- Failure to note the broader implications of choosing the right dietary lifestyle

A. Not understanding the book's objectives.

The findings described in the book are not solely based on the China survey data, even if this survey was the most comprehensive (not the largest) human study of its kind. As explained in the book, I draw my conclusions from several kinds of findings and it is the consistency among these various findings that matter most.

First and foremost, our extensive work on the biochemical fundamentals of the casein effect on experimental cancer in laboratory animals (only partly described in our book) was prominent because these findings led to my suggestion of fundamental principles and concepts that apply to the broader effects of nutrition on cancer development. These principles were so compelling that they should apply to different species, many nutrients, many cancers and an almost unlimited list of health and disease responses (e.g., nutritional control of gene expression, multi-mechanistic causation, reversal of cancer promotion but not reversal of initiation, rapidity of nutritional response, etc.). These principles also collectively and substantially inferred major health benefits of whole plant-based foods.

This earlier laboratory work, extensively published in the very best peer-reviewed journals, preceded the survey in China. These findings established the essence of what can be called biological plausibility, one of the most important pillars establishing the reliability of epidemiological research. [Biological plausibility represents established evidence showing how a cause-effect relationship works at the biological level, one of the principles of epidemiology research established by the epidemiology pioneer, Sir Bradford Hill.]

Unfortunately, this issue of biological plausibility too often escapes the attention of statisticians and epidemiologists, who are more familiar with 'number crunching' than with biological phenomena. The first 15-20 years of our work was not, as some have speculated, an investigation specifically focused on the carcinogenic effects of casein. It was primarily a series of studies intended to understand the basic biology of cancer and the role of nutrition in this disease. The protein effect, of course, was remarkable, and for this reason, it was a very useful tool to give us a novel insight into the workings of the cancer process. [Nonetheless, the casein effect, which was studied in great depth and, if judged by the formal criteria for experimentally determining which chemicals classify as carcinogens, places casein in the category of being the most relevant carcinogen ever identified.]

Second, this survey in rural China, based on a very unique population and experimental format (from several perspectives), resulted in the collection of an exceptionally comprehensive database that, to a considerable extent, permitted the testing of hypotheses and principles learned in the laboratory, both mine and others. By ‘testing’, I mean questioning whether any evidence existed in the China database to support a protective effect characterized by the nutritional composition of a plant-based diet. I was not sure what might be found but nonetheless became impressed with what was eventually shown.

The China project data afforded an opportunity to consider the collective interplay and effects of many potentially causative factors with many disease outcomes—the very definition of nutrition (my definition of nutrition is not about the isolated effects of

individuals nutrients, or even foods for that matter). The China project encouraged us not to rely on independent statistical correlations with little or no consideration of biological plausibility. In the book, I drew my conclusions from six prior models of investigation to illustrate this approach: breast cancer, liver cancer, colon cancer (minimally), energy utilization/body weight control, affluent disease-poverty disease and protein vs. body growth rates. Using this strategy, I first inquired whether a collection of variables in the China survey (ranging from univariate correlations to more sophisticated analyses) could consistently and internally support each of these biologically plausible models and, second, I determined whether the findings for each of these models were consistent with the overarching hypothesis that a whole food, plant-based diet promotes health—I could not discuss much of this rationale in a page-limited book intended for the public.

Most importantly, I cannot emphasize enough that the findings from the China project, standing alone, do not solely determine my final views expressed in the book. That's why only one chapter of 18 was devoted to the China survey project, which is only one link in a chain of experimental approaches. I was simply asking the question whether there were biologically plausible data in the China database to support the findings gained in our laboratory, among others. Because of the uniqueness of the China database, I believed that the evidence was highly supportive. One of the unique characteristics of this survey was the traditional dietary practices of this cohort of people. Mostly, they were already consuming a diet largely comprised of plant-based foods, thus limiting our ability to detect an hypothesized plant-based food effect—thus making our final observations that much more impressive.

Third, in the book, we summarized findings from other research groups for a variety of diseases to determine the consistency of our model with their findings, according to my principles and concepts. One of the most compelling parts of this exercise was the fact that so many of their findings, although published in good peer-reviewed journals, had been and were continuing to be ignored and/or distorted, a very disturbing and puzzling phenomenon. This posed for me the question, why? My participation in extensive reviews of the work of others during my 20-year stint working on or as a member of expert committees gave me a particularly rich opportunity to consider these previously published studies. There still is, and for a long time has been, an intentional effort at various levels of science hierarchy to denigrate studies that speak to the more fundamental biology of plant-based diets. The fact that there has been resistance, oftentimes hostile and personal in the lay community, speaks volumes to me.

Fourth, and most importantly, there is the enormously impressive findings of my physician colleagues, which came to my attention near the end of the China project data collection period and which were showing remarkable health benefits of plant-based nutrition, involving not only disease prevention but also disease treatment (alphabetically: Diehl, Esselstyn, Goldhamer, Klaper, McDougall, Ornish, Shintani--and many others since the book's publication: T. Barnard, N. Barnard, Corso, Fuhrman,

Lederman, Montgomery, Popper, Pulde, Schulz, Shewman). I cannot overemphasize the remarkable accomplishments of these primary care physicians. In effect, their work affirmed my earlier laboratory research. I should add that I knew none of them or their work during my career in the laboratory, thus was not motivated or biased to find ways to affirm their work.

It was the combination of these various lines of inquiry that made so compelling the larger story told in the book, at least for me. Denise mostly ignores these fundamental but highly consistent parts of my story. In that vein, I strongly believe that the findings of no single study in biology or even a group of similar studies should be taken too seriously until context is established. Biology is not for engineers and number crunchers, as important as they may be, because, compared to their systems, biological response is much more complex and dynamic.

B. The use of 'raw' univariate correlations.

In a study like this survey in China (ecologic, cross-sectional), univariate correlations represent one-to-one associations of two variables, one perhaps causal, the other perhaps effect. Use of these correlations (about 100,000 in this database) should only be done with caution, that is, being careful not to infer one-to-one causal associations. Even though this project provided impressive and highly unique experimental features, using univariate correlations to identify specific food vs. specific disease associations is not one of these redeeming features, for several reasons. First, a variable may reflect the effects of other factors that change along with the variable under study. Therefore, this requires adjustment for confounding factors—mostly, this was not done by Denise. Second, for a variable to have information of value (as in making a correlation), it must exhibit a sufficient range. If, for example, a variable is measured in 65 counties (as in China), there must be a distribution of values over a sufficiently broad range for it to be useful. Third, the variables should represent exposures representative of prior years when the diseases in question are developing. I see little or no indication that Denise systematically considered each of these requirements.

I should point out that when we were deciding to publish these data in the original monograph, we decided to do something highly unusual in science—to publish the uninterpreted raw correlations, hoping that future researchers would know how to use or not use them. We felt that this highly unusual decision was necessary because we were wary of those in the West who might have doubted the validity of data collected in China—we had several experiences to suspect this. But also, we believe that research should be as transparent as possible, simply for the sake of transparency, thus minimizing suspicion of hidden agendas. We knew that taking this approach was a risk because there could be those who, knowing little or nothing about experimentation of this type, might wish to use the data for their own questionable purposes. Nonetheless, we decided to be generous and, in order advise future users of these data, we added our words of caution—written about 1988—as part of our 894-page monograph. I also

have repeated this caution in other publications of mine. It seems that Denise missed reading this material in the monograph.

As I was writing this, I discovered this comment from a self-described professional epidemiologist (PhD, cancer epidemiology) on one of the blogs (A Cancer Epidemiologist refutes Denise Mingers China Study Claims due to incorrect data analysis - 30 Bananas a Day!)—a comment that is relevant to the point that I am now addressing in this response.

I do not know this person but did find her comment interesting. After reviewing Denise's critique, she wrote the following for her (Denise's) blog, only then to see it quickly and mysteriously disappear.

"Your analysis is completely OVER-SIMPLIFIED. Every good epidemiologist/statistician will tell you that a correlation does NOT equal an association. By running a series of correlations, you've merely pointed out linear, non-directional, and unadjusted relationships between two factors. I suggest you pick up a basic biostatistics book, download a free copy of "R" (an open-source statistical software program), and learn how to analyze data properly. I'm a PhD cancer epidemiologist, and would be happy to help you do this properly. While I'm impressed by your crude, and – at best – preliminary analyses, it is quite irresponsible of you to draw conclusions based on these results alone. At the very least, you need to model the data using regression analyses so that you can account for multiple factors at one time."

This blogger is making the same point that I am making but I am puzzled why was it deleted from Denise's blog?

Lest it be forgotten, the main value of the China data set is its descriptive nature, thus providing a baseline against which other data sets can be broadly compared, either over time or over geographic space. I must emphasize: the correlations published in our monograph CANNOT be blindly used to infer causality—at least for specific cause-effect associations having no biological plausibility. Nonetheless, they do offer a rich trove of opportunities to generate interesting hypotheses, relatively few of which have been explored to date. In contrast, using models representing biological plausibility, which was determined from prior research, I simply wanted to see if they were consistent with the China survey data.

For the sake of understanding the downside risk of using univariate correlations, I'll use this imaginary conversation involving a few correlations that Denise thought were relevant to her personal allergy to wheat, although many other examples from Denise's treatise could serve the same purpose.

Denise makes a point concerning a highly significant (but unadjusted) univariate correlation between wheat flour consumption and two cardiovascular diseases plus a couple other diseases. In doing so, she infers that wheat flour causes these cardiovascular diseases. She also makes the point that "none of these correlations

appear to be tangled with any risk-heightening variables, either." And further, she implies that I ignored this potentially important correlation, perhaps intentionally, because of my alleged bias against meat. I use this particular example here because others who very much dislike my views have pointed out on the Internet that this example cited by Denise represents evidence of my lack of integrity.

The conversation goes like this, after Denise reminds me of these univariate correlations.

"Denise, that correlation of wheat flour and heart disease is interesting but I am not aware of any prior and biologically plausible and convincing evidence to support an hypothesis that wheat causes these diseases, as you infer.

"Did you, by any chance, look for evidence whether there might be other variables confounding the wheat flour correlation, variables that change in parallel with wheat flour consumption? I presume you did because you said that 'none of these correlations appear to be tangled with any risk-heightening variables.'

"But just a minute, I found some, and they're all highly statistically significant ($p<0.01$ to $p<0.001$).

"Higher wheat flour consumption, for example, is correlated, as univariate correlations, with

- lower green vegetable consumption (many of these people live in northern, arid regions where they often consume meat based diets with little no consumption of vegetables). [By the way, Tuoli county data, to which you refer as my "sin of omission" intentionally were excluded from virtually all our analyses on meat consumption because this county ranked very high when meat consumption was documented at survey time, but much lower when responding to the questionnaire on frequency of meat consumption. That is, these nomadic people migrate for part of the year to valleys, where they consume more vegetables and fruits.]

- lower serum levels of monounsaturated fats (possibly increasing risk of heart disease?)

- higher serum levels of urea (a biomarker of protein consumption)

- greater body weight (higher risk of heart disease?)

"Interestingly, you might be interested to know that all of these variables are known from prior knowledge, i.e., biological plausibility, to associate with higher risk for heart disease.

“Denise, this is quite an oversight that could suggest the opposite conclusion from the one that you intended to convey. Or was this bias reflecting your personal preference for eating raw meat and avoiding wheat flour? Any thoughts?

“Why did you highlight this relationship as a key example of my “sin of omission”, being even more ‘troubling than the distorted facts in The China Study and the details that (I) leave out?’”

Incidentally, aside from Denise’s claiming there were no confounding factors, I might have taken her seriously when she posed a possible effect of wheat flour on heart disease, because it may be possible to gather prior evidence that could be considered as supporting the opposite point of view. In fact, this would be a proper use of univariate correlations, simply searching for those correlations that might hint of supporting evidence for such an hypothesis. If sufficiently convincing, then we could design a more analytical type of study. This exercise is called hypothesis generation, which is one of the virtues of the China data set. But Denise is doing something different, coming very close to almost randomly inferring causality without adjusting for confounding factors, without scanning the variables for analytical authenticity and without—to my knowledge—having prior evidence of biological plausibility for such an hypothesis.

Then, she uses this example as evidence of a “sin of omission” and a “distorted fact” on my part. Using these rather inflammatory words infers serious personal indiscretion on my part. Does she really mean this?

There are different ways of using univariate correlations in a database like this. It is not that these correlations are useless and should be ignored. Rather, it is a question of using them intelligently. By this, I mean first adjusting these correlations for confounding factors (if and when possible) then examining the individual variables of the correlations for authenticity. Depending on the reliability of these correlations, they may be used to guide whether a hypothetical, cause-effect model, perhaps having preliminary evidence of biological plausibility, is on the right track. The most critical expertise needed for their use is knowing the underlying biology, which is so often missing among trained statisticians.

The six models to which I referred in our book are those evaluated in this manner. Yes, when possible, I also used univariate correlations (along with statistical significance) in support of these models but only after we had preliminary supportive data for the model (only brief summarized in the book). Here are a few representative publications of those supportive data for the six models that we explored in our book:

Breast cancer (Marshall JR, Qu Y, Chen J, Parpia B, Campbell TC. Additional ecologic evidence: lipids and breast cancer mortality among women age 55 and over in China. Europ. J. Cancer 1991;28A:1720-

1727; Key TJA, Chen J, Wang DY, Pike MC, Boreham J. Sex hormones in women in rural China and in Britain. Brit. J. Cancer 1990;62:631-636.)

Liver cancer (Campbell TC, Chen J, Liu C, Li J, Parpia B. Non-association of aflatoxin with primary liver cancer in a cross-sectional ecologic survey in the People's Republic of China. Cancer Res. 1990;50:6882-6893; .Youngman LD, Campbell TC. Inhibition of aflatoxin B1-induced gamma-glutamyl transpeptidase positive (GGT+) hepatic preneoplastic foci and tumors by low protein diets: evidence that altered GGT+ foci indicate neoplastic potential. Carcinogenesis 1992;13:1607-1613).

Energy utilization (Horio F, Youngman LD, Bell RC, Campbell TC. Thermogenesis, low-protein diets, and decreased development of AFB1-induced preneoplastic foci in rat liver. Nutr. Cancer 1991;16:31-41:Campbell TC. Energy balance: interpretation of data from rural China. Toxicological Sciences 1999;52:87-94).

Colon cancer (Campbell, T.C., Wang G., Chen J., Robertson, J., Chao, Z. and Parpia, B. Dietary fiber intake and colon cancer mortality in The People's Republic of China. In: Dietary Fiber, Chemistry Physiology and Health Effects, (Ed. Kritchevsky, D., Bonfield, C., Anderson, W.), Plenum Press, New York, 473-480, 1990).

Affluent-Poverty Diseases (Campbell TC, Chen J, Brun T, et al. China: from diseases of poverty to diseases of affluence. Policy implications of the epidemiological transition. Ecol. Food Nutr. 1992;27:133-144).

Protein-growth rate:(Campbell TC, Chen J. Diet and chronic degenerative diseases: a summary of results from an ecologic study in rural China. In: Temple NJ, Burkitt DP, eds. Western diseases: their dietary prevention and reversibility. Totowa, NJ: Humana Press, 1994:67-118; Campbell TC, Junshi C. Diet and chronic degenerative diseases"perspectives from China. Am. J. Clin. Nutr. 1994;59:1153S-1161S).

As I previously said, one of my interests in the China database was simply to see if there was evidence supporting the health benefits of a plant-based diet for these various models (and many more). The fact that we observed a slew of statistically significant results supporting this proposition, especially for a dietary experience having such low total fat and animal based foods, was quite remarkable. Did every correlation among our 100,000 show the expected? This was my comment, verbatim, already published in our book (that Denise did not acknowledge in her critique):

"Do I think the China Study findings constitute absolute scientific proof? Of course not. Does it provide enough information to inform some practical decision-making? Absolutely. An impressive and informative web of information was emerging from this study. But does every potential strand (or association) in this mammoth study fit perfectly into this web of information? No. Although most statistically significant strands readily fit into the web, there were a few surprises. Most, but not all, have since been explained."

In summary, Denise's critique lacks a sense of proportionality. She gives (with considerable hyperbole, at times) the analyses of the China data more weight than they deserve by ignoring the remaining evidence discussed in the other 17 chapters in the book. The China research project was a cornerstone study, yes, but it was NOT the sole determinant of my views (as I have repeated, almost *ad nauseum* in my lectures). In

doing so, and except for a few denigrating remarks on our experimental animal research, she also ignores the remaining findings that I presented in our book. She seems not to understand what our laboratory research was showing. Using univariate correlations mostly without adjustment for confounding factors, qualification of variable authenticity, and/or biological plausibility can lead to haphazard evidence, subject to the whims of personal bias. Also, univariate correlations of this type can lead to too much emphasis on individual nutrients and foods as potential causes of events.

Also, as I already mentioned, she questions our omission of the Tuoli County data as if this was some sort of sleight of hand on my part (in addition to my comments above, I already explained this omission in one of my papers and on my preliminary blog). She over-interprets our very limited 'dairy' data which only includes 3 counties (of 65) that use a very different product from what we consider to be dairy. And she continues to characterize my views in reference to veganism and vegetarianism (I don't even use these words) as if I were motivated by an ideology instead of by my consideration of empirical data and biological plausibility.

Not only does Denise misrepresent and misunderstand the rationale for the science in The China Study, her choice of words do not facilitate what she hopes to achieve. Her overall message, often embellished with adjectives and subjective remarks, appeals to some questionable characters sympathetic to or subservient to the Weston A Price Foundation, a farm lobbying group whose advocates and apologists have accused me of being a "fraud", a "liar", a "buffoon" and (earlier) an associate of a "terrorist" organization. I doubt that this is what she wanted to achieve. These individuals, for much too long, have been carelessly using or even ignoring science to further their own interests, such as advocating for the use of a very high fat, high protein diet mostly consistent with the diet that has caused us so much difficulty.

This name calling means nothing to me personally but it does indicate their desperation with our message. They would be well advised not to use such tactics because it reflects on them, not me. Whether Denise intended this is not clear, but the results of her critique is clearly apparent.

I must repeat for emphasis that no single study (or even a group of similar studies) is perfect in its design, in its data collection or in its interpretation of results. From the perspective of developing a research career, I see two possible paths that a researcher may follow. One option proceeds from experiment to experiment by probing ever deeper into the details of one of those experiments that they may happen upon where precision of measurement matters deeply and where the findings can become useful at some future time--indeed, they may "happen upon" an observation that becomes their life's work very early in this process, maybe even at the outset.

A second option proceeds 'outwardly' to better understand the broader implications of a series of findings, or experiments. I did some of the first but eventually preferred the

second, taking each finding not as something to refine into ‘perfection’ but to ask whether it was sufficiently compelling to suggest the next obvious experiment that eventually might lead to an important network of findings. Having done both, I strongly prefer the latter option because the whole, indicated by a network of findings, is often far more useful than its parts. I also believed that this second option had more potential to meet the interests of the public who funded our research. I also am very much motivated by the fact that there are far too many individuals needlessly paying a heavy personal price in their health for not having access to information of this kind that could have saved their lives, a moral issue for me. Under no circumstances was I controlled by what my personal preferences might have been!

In the case of our project in China, I believe that its design, its uniqueness and its execution are virtually without parallel in its quality--thanks very much to my colleagues. However, as trained people know, making specific inferences about causality is not appropriate in a study of this kind. The concept of 'ecologic fallacy', wherein a univariate correlation is improperly used to diagnosed or to treat an individual person, is well known. In contrast, if one initially has a reasonably convincing and biologically plausible body of data and if the data are appropriately qualified, then using a study like to this to see if there is consistency, is appropriate This is appropriate in my opinion if the hypothesis being addressed represents a comprehensive causal effect where many factors are acting in concert and where there may be multiple ways of examining the data (e.g., multiple factors being consumed, multiple clinical biomarkers of factor tissue status, multiple methods of measurement and, perhaps, even multiple outcomes). This is what we did. We began with a collection of previously developed cause-effect models (previously published) that we could test for consistency with the China data. We found on balance considerable support in the China database for these models. As I've said many times, not all the evidence in the China database supported this conclusion, although the large majority did. To find this degree of consistency in a population mostly using a low fat, high fiber, whole plant-based foods with little or no processed foods—where I had thought that we would see little or nothing—was impressive. One cannot, as Denise has done, rely on univariate correlations to make conclusions, especially when they are focused on specific foods for specific diseases—it is too easy to find what one wants to find.

I know that this discussion between Denise and me is difficult to judge by readers of this exchange without having access to the raw data base and without knowing how to use or interpret it. Accepting this, therefore, I suggest that, in the final analysis, the reliability of any conclusion about complex cause-effect issues should be judged by its ability to predict health outcomes. In this case, the results of people using a diet of whole, plant-based foods, as shown by physician colleagues (previously mentioned, McDougall, Esselstyn, Ornish, Barnard, Fuhrman, et al) as well as by many of the readers of our book are nothing less than incredible. There is nothing else in medicine like it!

C. Denise’s failure to note the broader implications of choosing the right dietary lifestyle.

I suggest that those people who are so hostile to this message take another look at their reasoning. There is far more to this story than the interpretation of the scientific data alone. There are major issues of health care and health care costs, there are serious environmental issues that have not been adequately communicated to the public, and there are political, social and ethical issues that must be considered. Of most importance, there are people who deserve to hear this message—namely, the taxpayers who funded this work. For me to do anything less than to report on these findings is both immoral and unethical. In the current discussions about this issue, I would urge that it is vitally important that all of us keep these ideas in mind, while being very careful not to promote ideas simply for the sake of defending one's own personal preferences. I strongly believe that discussion of these issues focus outwardly for the sake of all of us, not just inwardly for the satisfaction of personal ego.

My greatest mistake throughout this process may have been our acquiescence to our publisher's choice for our book's title. We suggested 200 possible titles, not one of which was 'The China Study'. But when we objected, he said that we already had signed the contract and this was his right and responsibility. We felt locked in, especially because we had already explored publication with about 10 other publishers, some of whom had offered advances (one very large), if we did it their way. Because we had refused to accept their suggestions (including at least half the book as recipes, going easy on the references and 'dumbing down' the language), it seemed clear that we had no other choice than to go along with our new publisher who accepted our way of telling this story.

Obviously, the title of our book has been misleading for some because of the inappropriate weight suggested by the China project itself. When these rather novel data are considered both in reference to biologically plausible, multi-factor models of causation and in reference to the large body of other kinds of studies discussed in the book, the China project database becomes very important. But relying on the results of this study in isolation, especially when unadjusted univariate correlations are used, is not appropriate.

I should conclude by noting the suggestion of the professional epidemiologist, cited above, who suggested that ultimately Denise may wish to publish her findings in a peer-reviewed journal but who presently felt strongly that the current version would not be accepted. I concur.