corres - Winston

UNIVERSITY OF MINNESOTA
TWIN CITIES

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August 17, 1981

Mary Winston, Ph.D.
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Dear Friends:

This is a letter confirming the mailgram which was delivered several days after it was promised. In it I explained my confusion, due to recent extensive travels, about the purpose of the August 10th meeting and my impression that it was concerned primarily with the Diet in Childhood statement rather than a review of all American Heart diet statements and positions. In it I question the appropriateness of a superficial review including five-minute statements by "external" and "internal" experts on different aspects of the so-called diet/heart/lipid "hypothesis." This is inappropriate after 20 years of intensive and expert American Heart Association review and its well-established public recommendations about which no significant new evidence countermands any of those recommendations. I indicated that a thoughtful review of the issue would require the updated Grundy statement, incorporating the extensive input of experts in the New York meeting in June 1981, and subsequent useful suggestions to Dr. Grundy from other experts including Stamler.

Though in the mailgram, I question the purpose and orientation of this particular meeting, I enthusiastically endorse the idea of a new and separate statement for the lay public on all risk factors combined. This would be appropriately accompanied by a parallel new statement to physicians in which some of the dietary issues might usefully be updated such as the diet/cancer relationships and the effects of fiber, alcohol, sodium and potassium.

I went on to comment in detail on the Diet in Children and Adolescents statement as representing substantial progress on the part of the youth group and with particular enthusiasm for the well laid out recommendations for diet in youth.

Minor modifications and emphases in language were proposed as follows: Page 1, paragraph 1, sentence 2 might be modified to read as follows: "evidence of this association has been derived from many approaches including epidemiology,

human pathology and experimental pathology, and their congruence appears sufficient to imply causation."

Page 1, paragraph 2, sentence 4, I suggest change in emphasis on HDL cholesterol. It should be indicated as simply a measurement method while the true predictor is HDL, the lipoprotein. The statement as it now stands reinforces the common, and unfortunate, misconception that there is a "good and bad cholesterol." I suggest changing the wording as follows: "epidemiological studies document that risk rises as the cholesterol component of LDL rises until middle age, after which, in the United States, the risk is more strongly associated with decreasing HDL levels."

Page 2, paragraph 1, sentence 2 is now rendered obsolete by the New England Journal of Medicine article of Shekelle in 1981 and might be written as follows: "Correlations between individual diets and individual plasma cholesterol levels, within high risk populations, have now been demonstrated to exist when care is taken to reduce the variability of measurement of diet and plasma lipids."

Page 2, paragraph 3. I suggest be rewritten as follows: "The conflicting results which show strong diet and blood lipid correlations between populations, and weak ones between individuals within populations, are largely explained by the variable and inaccurate means of assessing individual diet as well as the generally high fat diets consumed in the United States. In addition, individual and technical variability in plasma lipid measurement further attenuates the correlations within such high risk populations.

Page 2, paragraph 4 and page 3, paragraph 1. In this issue Dr. Weidman knows that I prefer less emphasis on individual differences of blood lipid response to diet change. I do not believe this "hypo- or failed response" is well documented, beyond clinical impression. Our work here currently, as well as Fred Mattsons', shows that surely not more than 10% of individuals can be characterized as "hypo-responders" to diet. The vast majority respond quite predictably when the relationship is examined under controlled conditions. Thus, I respectfully suggest a rewording of that paragraph on page 2 along these lines: "A small proportion of people may respond unpredictably, or fail to respond, to experimental or therapeutic diet changes, presumably through different metabolic pathways. But compliance is the usual cause for discrepancies."

Page 3, The statement about cancer requires an update, and I suggest something along the following: "Associations between diet, blood lipid levels and cancer are inconsistent and appear significant only for colon cancer in men with low cholesterol levels, and not for women. Moreover, populations having low cholesterol levels, as well as low coronary disease rates, are not characterized by high colon cancer rates. Furthermore, the risk of bowel cancer attributable to low cholesterol in men is extremely small compared to the risk of coronary disease in men with high cholesterol. Finally, the lack of congruence between

the clinical, experimental and population evidence, as well as the lack of clear mechanisms, leaves this issue quite unsettled. Even if the mechanism were an individual capacity for efficient bile acid excretion, with lower plasma cholesterol and higher cancer precursors in the bowel, avoidance of a high fat diet might very well still be advisable."

In the summary paragraph I suggest placing a period after children, and adults, in paragraph 3. As previously mentioned, I think the dietary recommendations on pages 4-6 are first rate!

Again, my apologies for missing an important meeting. Let me know if there is anything I can do in regard to contributions to any edited outcome of that meeting.

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB:blh

bpc: J. Schoenberger
J. Stamler
W. Weidman
S. Grundy
D. Harrison

√ Sent 8/18/81 ejo

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August 24, 1981

Dr. Mary Winston
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Dear Mary:

These are comments on the updated draft of Dr. Grundy's report on Treatment of Hyperlipidemia, a Statement for Physicians. I am still a bit uncomfortable with the arbitrary and dichotomous definition of hyperlipidemia. How much stronger would be the statement, and how much more salubrious the educational influence, if we were to indicate that hyperlipidemia is an interaction between powerful dietary influences and various but widespread degrees of genetic susceptibility and different intrinsic regulation. How much nicer it would be to introduce this material with the suggestion that all Americans need some dietary counsel, but that the statement is directed to those with specific, if arbitrarily defined, elevations of blood lipids.

Page two, paragraph two: typo omission of the word "of" in the second sentence, "diet induced reversal of atherosclerosis".

I think I have reacted before to paragraph three on page two. I find it a bit tiresome and negative to hear so repetitively about "the absence of a definitive clinical trial," without such qualifying statements that it has been agreed that such is not feasible, because of the design requirements of numbers and resources.

I also suggest, in the first paragraph, page three, that the credence given the National Research Council report is totally unnecessary, and in no way strengthens our statement. I don't understand why an organization with as distinguished a review process as the American Heart Association, would regard that report as having any new or firm scientific basis, or being anything other than a grossly politically, economically motivated report. It does not strengthen ours to enhance the NRC credibility.

Paragraph two, page three -- I'm uncomfortable with seeing the much mis-used cliche, "impact on" instead of the correct English "influence on", or "the risk factors having an impact on dietary treatment". But I'm enthusiastic for bringing into the discussion the influence of other risk factors on the decisions for treatment.

Paragraph one, page four I find not a particularly helpful statement for the practitioner: "It is important to know how the values obtained in a specific laboratory relate to true cholesterol concentrations". Does the practitioner have any recourse?

I am puzzled by the second paragraph on page seven, in which it says "In obese patients with hypercholesterolemia, particular attention should be given to restricting saturated fat calories because this will produce the greatest lowering in LDL cholesterol." Is not the emphasis misplaced? Restricting saturated fat calories will produce the greatest lowering in LDL cholesterol at any weight. Isn't the special message we're trying to get across here that weight reduction gives an added and apparently sustained effect to change in composition. As given here it is a misleading statement.

Page eight, paragraph two, sentence one -- cholesterol is given as plural. Was this intended? ("saturated fats and cholesterols").

The cancer statement at the bottom of page nine should surely be revised in conjunction with Scott Grundy's other recent report. I feel now it is a weak and negative statement, which detracts from the overall impact of the message. I think it should be stated clearly that there is no evidence that a shift of the nature we are proposing, in individuals with cholesterol levels above the 90th percentile, or a shift of 10 or 15 mg. percent in the population median and distributions, would have any negative effect, and I see no reason to suggest that it might, as Scott does. I think that the statement about "several epidemiological studies suggests that very low levels of cholesterol, etc." should be redone. These are the points that I would list: epidemiological studies are inconsistent, with the possible exception of agreement on a relationship between low serum cholesterol levels and bowel cancer in men. The Associations found in no way meet full criteria of causal inference. The attributable risk from low cholesterol for bowel cancer is infinitesimally small compared to the attributable risk for coronary disease with elevated cholesterol values, and epidemiological evidence suggests no excess of cancer deaths in whole populations with low total cholesterol levels.

I think perhaps a most damaging statement in the report is unnecessary, academic and defensive: "The possibility that cholesterol lowering will be shown at some future time to affect health in a negative way cannot be excluded". I don't understand this sort of statement in an authoritative guide from the American Heart Association. If a physician wants to mention these things as possible with an extremely unusual experimental diet or drug use, that's fine. But the statement as is, I believe, is not appropriate in this guideline to physicians.

Page one, paragraph one: "Our common understanding of 'a risk factor' is an independent risk factor". There are internal inconsistencies within that paragraph, in which we say at one place, it is not an independent risk factor, and in another, it is a risk factor.

The rationale for treatment of hypertriglyceridemia appears, to me, a bit weak. Would it be stronger to say that hypertriglyceridemia is a departure from idealized levels and gives a clue as to the mechanisms and therapy required for reducing blood lipids. Rather than reverting to authority as in, "Many investigators believe that serious consideration should be given to treating hypertriglyceridemia", why not stick with the facts? It is an abnormality associated with excess risk through unclear mechanisms, and therefore, should be treated, irrespective of the lack of demonstration of its independent risk. Is it not similar to the arguments for treating obesity. I am uncomfortable with coming back to authoritative arguments when the evidence gets weak, and particularly when it isn't necessary.

Page 13 -- I am interested in the evidence that suggests "a low fat diet may be required to prevent pancreatitis in patients with severe hypertriglyceridemia". That seems to be a very important recommendation, but I am unaware of studies which establish this relationship.

The paragraph does not contain the perhaps more relevant idea that carbohydrate raising of plasma triglycerides is usually a temporary phenomenon.

The introduction of a new term, "integrated levels of triglycerides", perhaps requires explanation. What is the evidence that "the area under the curve" is so affected?

Page 14, paragraph one: HDL. I am still concerned that Dr. Grundy fails to always distinguish between individual and population risk. The evidence which now exists to support the view that HDL cholesterol fraction is a significant predictor of CHD risk, should be qualified to older individuals, within high risk cultures. The evidence is to the contrary in populations; there is little or no relationship between population levels of HDL and population risk or rates of coronary disease.

After decades of trying to get rid of the term "the normal range", we find it creeping into this report in the last paragraph on page 14. This falls right into the old problems of laboratory dictated normal ranges. There is still no clear idea whether we're talking about statistical norms or normality in terms of relative freedom from disease risk. A qualifier should be entered, preferably speaking in terms of disease risk rather than of statistical norms.

I like the qualifier at the end of paragraph one on page 15, but would prefer to have it up front in the report. Again, in paragraph two on page 15, we use the old saw "it has not been proven". I believe that under no circumstances should that statement appear in an American Heart Association recommendation. I prefer completely omitting the statement, but a change in wording such as "it has not been experimentally established that" would get away from the unhappy and misleading and undefined cliche of "unproven". Further on in that paragraph: "the potential dangers associated with an excessive intake of alcohol must be carefully balanced against the possible benefit of its raising HDL levels" is, I believe, nonsense and should be stricken. I'm sure we would never want to imply that alcohol was healthy, or was healthy because of that particular mechanism, at this stage of our knowledge. I thought we had long discussions about the different kinds of HDL, and what we don't know about so-called beneficial effects of alcohol or the different HDL subfractions. This gives credence to an effect we can't defend.

Recommendation #1 in my view says nothing. Recommendation #3 goes to a specific value rather than the 90th percentile, which differs by age and sex. Is that not an inconsistency?

Recommendation 3.2 -- what is an "unsatisfactory" diet response? An absolute value rather than a percentile value is also used for triglycerides. That is fine, but should we not be consistent. Again, in 3.4 -- what is an "unsatisfactory" diet response?

The summary statement "Without absolute proof" must, by all means, be stricken. In my view, it is positively medieval to suggest that there is such thing as "absolute proof", as equivalent to absolute truth. "Without more complete demonstration that changes in HDL cholesterol can be induced" might be an appropriate statement.

The first sentence in the summary paragraph is long and needs to be redone with the subject put up front rather than at the end.

Paragraph two summary: I don't see the clause "based on data on the natural history of CHD" as particularly appropriate. In fact, I have some concern about the summary statement. Why are its contents not put in the recommendations, rather than as a "soft underbelly" to the recommendations. The statement "It seems warranted that cigarette smoking should be discouraged" is weak. The last sentence would better have added to it "by pharmacologic and non-pharmacologic means, including weight reduction, increased physical activity, and salt restriction."

I am also concerned by the statement "the American Heart Association believes". The American Heart Association recommends! Appendix A, sentence two -- "Normalization of plasma lipids" -- this is the old problem. Would not "Reduction of plasma lipids to levels compatible with reduced coronary risk" be more appropriate than the old clinical saw of "normalization".

Many thanks for the chance to see this. It is almost there and will be a classic!

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB:blh
pc: S. Grundy
bpc: J. Stamler

Sent 8/25/81 LB

pc: R. Luepker sent 8/25/81 LB

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August 24, 1981

Dr. Mary Winston
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Dear Mary:

This is my running comment on the Dietary Sodium and Hypertension statement of Bill Insull, revised and sent to us, with your memo, on July 21.

It seems to be an improved and sound statement, bound to be useful. Enclosed is my running commentary.

I continue to object, on page one, sentence two, to the negative academic statement "the causes of essential hypertension are unknown". This is so comfortable to say, and yet so misleading. Why not indicate the great deal that is known, or drop the sentence entirely. It simply gives so much strength to the argument of those who suggest that we should do nothing. The general introductory statement and conclusions are very strong and upbeat. I am glad to see that we've returned to the grams and milligrams, and that we have detailed information on their conversion to milliequivalents in the footnote. I'm happy to see the definitions, even though arbitrary, for hypertension. The section on evaluation and measurement is strong and useful.

I see no significant addition to the strength of the statement by the last sentence on page three. Again, it is academic and defensive, and I see no special reason for it.

Page four, the latter part of the first paragraph on the metabolism of sodium -- the following statement might better be qualified: "However, increased blood pressure, hypertension, occurs at the higher levels of sodium intake, as described below". I suggest: "tends to appear in a significant number of adults in populations at the higher levels of sodium intake, as described below". Page five, paragraph two, I am puzzled by the statement "The sodium requirements for children and adults have not been established". Again, that is such a negative and academic statement, and might better read as follows: "The sodium requirements for children and adults are defined by these losses just considered, and by the findings in populations which thrive on extremely low levels of sodium intake."

Later on in the same section, there is an implied prescription of 6 grams of supplemental salt! I believe that needs to be tightened up. When, if ever, is a salt supplement required? Certainly, on the usual high-salt American diet, athletic teams have found it progressively less needful to provide any supplement, only water sufficing under most conditions.

At the top of page seven, I believe the word "incidence" is inappropriately used where Bill means the frequency or prevalence of adult hypertension is below three percent in those populations. I also question the use of Western cultures in this context; we're talking about affluent and industrial populations, east or west. We're not talking about an increased incidence of hypertension with advancing age, because there are very few studies on the incidence of hypertension. We're talking rather about the frequency or prevalence of adult hypertension.

There is a typo in line ten of page seven, where I think Bill means 25 grams of salt, rather than 2.5. There again, "incidence" is not entirely properly used -- "there is a high incidence of stroke, and there is a high frequency of hypertension" is correct. I've never seen any incidence studies of rates of new development of hypertension in Japan, which require a time-based population rate. In the next sentence about Newfoundland, the correct term "prevalence" was used.

The last sentence in the first paragraph on page seven probably should be qualified, "recent studies within populations in the United States and other countries have, due to greater precision and repetition of measurements to reduce variability, more consistently demonstrated a relationship between individual salt intake and individual blood pressure levels." It is now an overstatement and does not clearly distinguish individual from population correlations.

In the next sentence, again, we refer to Western cultures rather than to affluent industrial cultures. Again, page ten, paragraph two, line three -- the term "incidence of hypertension" is inappropriately used, as on line four. Page 11, line three I suggest that the word "should" be replaced by "may".

I am enthusiastic about the recommendations for individuals, for food manufacturers, for labelling and for research. I am pleased that Bill found some of the material in my recent review of value in this regard.

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB:blh
pc: Dr. William Insull ✓sent 8/25/81 HB

Collins - Winston

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December 22, 1981

Mary Winston, Ph.D.
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Dear Mary:

I thought that your December 3rd letter to Ann Collins was beautiful. It is too bad she didn't consult and discuss before taking her action. Her action is in a sense a declaration of disagreement, which is not good.

It might be useful to send our Committee the detailed comments of her letter to you and what she was taking issue to specifically.

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB/jml