Corresp. C.F. Sing
Ms filed under
Risk factors - Lipid
Genetics

UNIVERSITY OF MINNESOTA
TWIN CITIES

Laboratory of Physiologic Hygiene
School of Public Health
Stadium Gate 27
Minneapolis, Minnesota 55455

FILE COPY

November 10, 1978

Dr. Charles F. Sing
Professor, Department of
Human Genetics
University of Michigan
1137 E. Catherine St.
Ann Arbor, Michigan 48109

Dear Dr. Sing:

I have appreciated your letters, your calls, your papers and your recent conversation with Dr. Prineas. We certainly hope here that it will be possible to have you visit us long before next spring. I would like to see our "mutual education" proceed expeditiously. If you anticipate a visit to Dr. Weidman before next spring please let me know.

Can you help me with the following comments and questions?

I am wondering if your statement is really the appropriate consideration, i.e., your idea that it's quite impossible for populations to be identical, what with the possible combinations of I believe you said 56 genes and several alleles which are probably involved in inherited lipid regulation through the apoproteins. How much influence or how many genes, and how do we know? Is it not likely that the more genes involved, the more likely we are to get a "normal distribution" - which should be complex but generally similar between very large heterogenous populations? How is it possible to estimate the genetic influence on such population means and distributions? How can we best study these matters?

I have thought for some time to study this in populations having "minimal load" and "maximal load" of the environmental factors. I also have thought it would be somewhat revealing to feed extreme diets experimentally to people at the extremes of baseline lipid levels, and to measure the extent of environmental influence possible. Would it be possible to design studies in Finland and Japan, which contrast so widely in diet and in their distributions of blood lipids?

Now I have some specific comments about your August 18th draft which, though very useful, will be very difficult for a nongeneticist to read and appreciate. In my view it also tends to stir controversy by its rather negative, almost derogatory, statements about "statistical studies about populations". Though you seem to have cogent reasons from a long experience to deprecate the importance of such studies, I wonder if you do not protest too vigorously. I personally would suspect that such studies might very well be used to increase our understanding of genetic-environmental questions and

believe they have already done so, particularly in regard to the Japanese immigrants.

I wonder if you are fully aware of how "statistical findings" can indeed, and certainly should, lead us to causal inference.

I guess I don't entirely understand your imperative "imperative" of the last sentence in paragraph 1, page 2. I suspect you can enlighten me when you visit us.

Part of my education will be to understand why the term "phenotype" is used for such a measurement as age.

Isn't your conjuring up the spector of "health planners" a little unfortunate? If such people really exist, maybe we should smoke them out, but I think it may appear a little paranoid, or be a little too political, to talk about people plotting our health. I am not sure that there are such people and anyway the term is derogatory. Be very specific in identifying your adversaries if you have any.

Of course, any investigator must be enthusiastic for your general goals of predicting population disease patterns and the continued search for subgroups which help the understanding of etiology.

There is a jargon problem for nongeneticists throughout this manuscript - which should be relieved if the article is to be published in a multidisciplinary proceedings.

Your sentence at the end of page 2 may be a little pedantic. Such positive assertions are a bit dangerous if unaccompanied by a fine supporting argument (or perhaps a little humor).

I like your indication on page 4 that the populations used for study often determine our views of issues and may result in misuse or confusion. That is a point which I constantly emphasize that bias from training and experience in select groups influences our views, which should not always be extrapolated to the larger problem. This is why I am hopeful that geneticists can teach us what they know and also be exposed to population issues. Moreover, public health decisions at times supplant academic precision, when they are very obvious, such as the dangers of smoking against the exaggerated claims, of some doing twin studies, of the importance of constitutional and genetic differences between smokers and nonsmokers.

On page 8, figure 3, I guess I don't understand at all the relation of the "intervening phenotypes" to cardiovascular "fitness". "Cardiovascular fitness" is a term reserved in <u>our</u> jargon for the ability to perform aerobic work. You will therefore be quite misunderstood on this point. On page 8, paragraph 2, are there really any "population studies of randomly selected individuals". This is almost unheard of (though we have a few such studies here). Defined populations are rarely random samples.

Neither overeating, sedentary living nor cigarette smoking are very strong contributors to "extreme cholesterol levels", so you have a large problem there. There is also no association between such levels, and, again, "cardiopulmonary fitness" (in terms of aerobic work capacity). It looks as if you should continue your conversations with us, Fred Epstein, and Bill Harlan, as there may be a considerable misreading on your part of the findings of cardiovascular epidemiology. Also, are you ignoring the congruence of evidence which leads very strongly to causal inference in these correlations, that is, congruence between results in experimental, clinical and population studies?

Page 12, I wonder if you would not like to do some calculations and then reconsider your attribution of cross-sectional age trends and total serum cholesterol to differential survival. I think you will find that such is not likely to contribute very much to those distributions. Just make a few models and work it out.

I hope to get back to this rather long article as it is heavy going for a nongeneticist, but fascinating.

For your article #2, presumably the one given in Chicago, you have indeed misquoted as well as misunderstood me and Jerry Stamler. You continue here to misuse the term "fitness" which has a very specific meaning. Why not use the terms that we use, such as risk of coronary event? Again, there is little association of the variables you mentioned in paragraph 1 with cholesterol levels in man.

Under no circumstances does my observation of the mass influence of habitual diet suggest "that genes contribute trivially to the determination of the response of an individual's cholesterol level". Where do you find that? In addition to that sentence being an anachronism, the two simplified models to which I invited your specific criticism indicate the very prominent nondietary (presumably largely genetic) contribution to regulation of individual cholesterol levels and attempted to show in contrast the very important environmental (dietary) contribution to population differences in cholesterol levels. Your comment doesn't really improve understanding or relieve controversy.

The argument of George Mann about the lack of effectiveness of "diet therapy" is not "in contrast" to my view, it is simply irrelevant to it and yet these two views are inappropriately juxtaposed. I nowhere talk about "diet therapy" anyway; I talk about habitual diet as it may have existed for decades (or centuries) in important natural experiments in contrasting cultures from which we derive many of our data and our impressions and recommendations.

I do hope indeed that my arguments (and others') will "benefit from knowledge about the role that genes play in the general population"; that is why I sought you out in the first place. Of course, I did not seek to be set up as a straw man nor to be labeled an evangelist which would be

inappropriate to our stimulating dialogue. We both have some conceptual views of considerable importance and validity, aside from any fervor in portraying them. To call people fanatic is to excuse not listening to their argument. This we do not wish.

Please keep in touch. We will finish an important site visit on December 14th and would welcome your visit anytime thereafter.

Cordially,

Henry Blackburn, M.D.
Professor and Director
Laboratory of Physiological
Hygiene

HB:pwl

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October 11,1978

Reply on Page 11/10

Dr. Henry Blackburn
University of Minnesota
Laboratory of Physiological Hygiene
School of Public Health
Stadium Gate 27
Minneapolis, Minn. 55455

Dear Dr. Blackburn:

Attached please find the two manuscripts which I referred to in our short conversation on Monday. Please forgive me for trying to tell you everything I know in five minutes. I feel it is very important you have an opportunity to see these papers before they go to press because I have referred to your work as a point of view which does not take into account the role that genetic variation plays within the population. I hope that I have not misread you.

One paper will appear in the volume on the Genetic Analysis of Common Diseases to appear shortly after the first of the year. The review of factors which predict serum cholesterol in the general population will be a part of the symposium in Chicago next week.

I will look forward to hearing from you about when we could get together to discuss risk factors in cardiovascular disease. I frequently visit Rochester as a part of my collaboration with the Mayo. It would be relatively easy for me to stop over in Minneapolis on one of those trips. If you are passing through Detroit on the way east it may be more convenient for you to visit in Ann Arbor. Either arrangement would be perfectly acceptable to me. I will be looking forward to hearing from you.

Sincerely yours,

Charlie

Charles F. Sing
Professor

CFS:mlw

SING

September 9, 1978

Dr. Charles Sing
Dept. of Human Genetics
University of Michigan
Ann Arbor, Michigan 48108

Dear Dr. Sing:

I am wondering whether my enthusiasm for our collaborating on the interaction between genetic and cultural factors in mass hyperlipidemia was too much for you. I look forward to a reaction. Maybe we could arrange to get together at the American Heart meetings in Dallas in November?

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB:pwl

SING

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UNIVERSITY OF MINNESOTA
TWIN CITIES

Laboratory of Physiological Hygiene
School of Public Health
Stadium Gate 27
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4 August 1978

Dr. Charles Sing
Dept. of Human Genetics
University of Michigan
Ann Arbor, Michigan 48108

Dear Charles:

I am very grateful for your contacting me and to Bruce Kottke for recommending that we get together. Fred Epstein has recommended this for many years.

You will see from the enclosed that I am one of those prime "exponents" of a public health,mass intervention view. You will also see by my "teaching models" that I am trying to do the same thing as you in conceptualizing these issues for our colleagues. You will also note that I am extremely naive in your area.

What I think would be a most productive outcome of our exchanges, after you have summarized your experience for the fall conference and have reviewed my attitudes herein, we might try together to translate this question for our colleagues and the public. I would dream of a joint editorial for Circulation.

Of course, there are many links missing: our ability to identify genetic components, to modify and determine the influence of modification on the intervening variables. I have made the quantum leap between population distributions to the potential for prevention - based on common guidelines of causal inference from powerful, consistent and congruent associations. There are a number of other holes in the data. For example, I enclose our recently compiled distribution of total serum cholesterol on a continuous basis from cross-cultural studies combined. This is unpublished and I guess we will have to wait for Dr. Keys' publication next year of the ten-year monograph.

Another approach I have thought of to help separate the effects is, again, a naive experiment. I've proposed to do it for 20 years and have not yet. Could we not learn something about the limits of the inherent factors by "ideal" feeding experiments: use the most cholesterol-raising diet in individuals with totally clear family history and low lipid profiles. Conversely use a maximal cholesterol-lowering diet in individuals with clear-cut inherited lipid metabolic disorders? Would not the distributions reached and changes made in distributions help us better identify the patterns? How best to design such experiments?

I think it would also be useful to model the various effects on population distributions of cholesterol of different diets among populatons with different frequencies of clear-cut inherited characteristics of lipid disorder.

We will need in summary to explain how even the very large inherent contribution to lipid regulation (and blood pressure regulation) within cultures does not negate public health importance of favorable or unfavorable environmental stress on the inherent susceptibility. We also need to take in consideration whether threshold effects exist for diet effect in mass, for cholesterol levels and risk and in terms of salt intake and pressure.

If we can weigh all these factors with teleological reasoning: i.e., man's evolutional adaptation to scarcity, to habitual physical activity, to rare meals of wild game, with fine salt-retaining mechanisms from salt scarcity, all this would make a nice package.

In addition to my ramblings you might want to peruse Jerry Stamler's similar soundings in the June 1978 issue of Circulation.

Cordially,

Henry Blackburn, M.D.
Professor and Director

HB:lgr

Enc: Geriatrics reprint
Levy ms.
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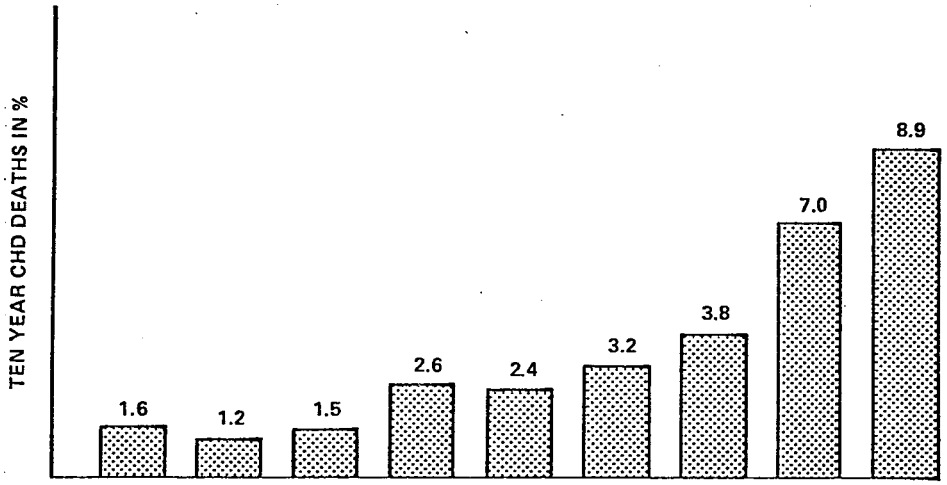
THE SEVEN COUNTRIES STUDY
TOTAL SERUM CHOLESTEROL AND CHD DEATHS



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