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John H. Weisburger, M.D.
Vice President for Research
American Health Foundation
Dana Road, Valhalla
New York, NY 10595

Dear Dr. Weisburger:

Response to your letter and enclosures sent last December is much delayed by the fact that I left here December 4th for Europe and only now have returned to find your communication in the accumulated mail.

Of course I know that the variety of neoplasms is legion and cancers in different sites may be initiated and promoted by quite different factors. Still, there are certainly some common features and it is not at all clear to me that cancers in different sites are metabolically totally unrelated. But this is not the issue in regard to the observations reported in The Lancet.

As you know, there has been a rather uncritical explosion of enthusiasm for the idea that HDL cholesterol is the enemy of coronary heart disease and the higher the concentration of that substance in the plasma the greater should be the cause for rejoicing. It does seem to be true that persons with clinical coronary heart disease tend to have average concentrations of HDL cholesterol in the plasma somewhat lower than the average for persons of the same age and sex who are clinically well, this tendency being noted, at least, in middle age and younger persons.

So it was interesting, and perhaps important, that the tendency was trivial when the follow-up was 25 years and the end point was death. And when comparison was made of the 1953 HDL cholesterol values of the men alive in 1978 with those who were dead by that time there was no difference at all in this parameter. More detailed analysis of the data turned up the surprising fact that the men destined to die from cancer had, on the average, higher plasma HDL cholesterol values at entry than the men in any of the other groups --survivors, men dying from coronary heart disease, men dying from all other causes.

I did not claim or intimate anything about cause and effect. The main conclusion was: "a high level of alpha cholesterol may be a mixed blessing for long-term survival," and: "Consideration of CHD only and follow-up on only a few years may greatly distort evaluation of the overall long-term significance of HDL cholesterol concentration in the plasma."

From the information at hand we cannot speak with any confidence about mechanisms and what causes what. Still, it is possible to speak about "betting odds" and actuarial probability and that is not without interest. Currently we are nearly finished with the 24-year follow-up of over 900 men we examined in Finland in 1956 with the measurement of HDL or alpha lipoprotein cholesterol measurements included in the examination. The other investigators who have been reporting on this subject have concentrated on coronary heart disease, not death, and none has as yet material with anything like the long follow-up periods we have here in Minnesota and in Finland. We shall see.

Now to return to the question of cancer. I do not claim or assume that all neoplastic diseases are alike in the biochemistry of pathogenesis. It is interesting to speculate, however, on the idea that some cancers tend to be associated with high levels of HDL cholesterol long before there is any indication of cancer while other cancers have no such tendency. If that is the case, in the "mixed bag" of cancers that killed 32 of my subjects it would follow that some of those cancers must have had a much stronger tendency to be associated with high HDL cholesterol than the average for the cancer victims. My material is too small to attempt the analysis along that line but this is something to think about when more adequate numbers are available.

I am sending a copy of this letter Dr. Wynder. From early May until mid-summer, and then after the first of September, I shall be at "Minnelea," 84060 Pioppi (SA) Italy.

Again, thank you for the reprints and your interest.

Sincerely,

Ancel Keys

AK/js