

## **Session 5**

### **Lecture : Molecular Epidemiology**

**Controversy :  
Should INH be used as monophylaxis in TB?**



## LETTERS TO THE EDITOR

RE: "THE LEGACY OF EPIDEMIOLOGY IN THE DEPARTMENT OF SOCIAL AND PREVENTIVE MEDICINE: A COMMEMORATION OF THE SESQUICENTENNIAL OF THE STATE UNIVERSITY OF NEW YORK AT BUFFALO SCHOOL OF MEDICINE AND BIOMEDICAL SCIENCES," "CURRENT PROBLEMS THAT ARE LIKELY TO AFFECT THE FUTURE OF EPIDEMIOLOGY," AND "TOWARD AN INTEGRATED APPROACH TO MOLECULAR EPIDEMIOLOGY"

The recent issue of the *Journal* (volume 146, number 11) commemorating the 150th anniversary of the Buffalo School of Medicine in New York included a number of interesting observations on the development of epidemiology. We are concerned, however, that some of the authors misunderstood our assessment of the choices and prospects for epidemiology (1, 2). Three papers in this commemorative issue correctly ascribed to us a belief in the importance for epidemiology of social and other contexts (3–5). At the same time, two of these papers misread us in suggesting that we hold no interest in molecular and biomedical epidemiology (4, 5), and the third misread us in suggesting that we do not endorse a continued emphasis on the development of rigorous methods (3).

On the contrary, we hold that epidemiology should—indeed must—learn to encompass multiple levels of organization, from the societal to the molecular. Rather than diminishing molecular epidemiology, we propose its further development and integration into studies of higher levels of organization. As for methods, we underscored a substantial development of methods as a necessity for realizing an epidemiology based on this paradigm. We believe that the search for rigorous methods must be intensified, but by broadening it to consider other levels of organization instead of restricting the focus to individual-level studies.

Perhaps confusion arises because we chose the term "eco-epidemiology" for the paradigm we advocate. The connotation in our usage is, to be precise, in Haeckel's original biological sense of ecological (or "oecological") organisms that interact with multilevel environments; it is not merely shorthand for groups or grouping (6).

For us, the potential of eco-epidemiology will be demonstrated by analysis of determinants and outcomes at different levels of organization: within and across contexts (by using new information systems), at the individual level (by exploiting risk factor epidemiology), and in depth at microlevels (by using new biomedical techniques). Hence our metaphor of Chinese boxes, which we described as "a conjurer's nest of boxes, each containing a succession of smaller ones" (2, p. 675). Preventive possibilities at all levels need to be considered, from contextual to molecular, to find efficacious levels of leverage.

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### THE AUTHORS REPLY

We thank Drs. Mervyn and Ezra Susser for clarifying their views on molecular epidemiology, and we agree with their comments (1). Our intent was to illustrate that there was concern in the field regarding the growth and direction of epidemiology but not to ascribe to Drs. Susser negative attitudes toward molecular epidemiology. We cited the articles by Susser and Susser (2, 3), Pearce (4), and Shy (5) to emphasize the need to draw more of a balance between modern risk factor epidemiology and population-based approaches that are closely linked to the historical roots of the discipline.

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**RE: "SEX DIFFERENCES IN RISK FACTORS FOR CLINICAL DIABETES MELLITUS IN A GENERAL POPULATION: A 12-YEAR FOLLOW-UP OF THE FINNMARK STUDY"**

On the basis of 12 years of follow-up of 11,654 Norwegians aged 35-52 years, Njølstad et al. (1) recently reported that high density lipoprotein (HDL) cholesterol, controlled for potential confounders, was inversely associated with type 2 diabetes among women but not among men. These findings of a sex difference in HDL cholesterol as a protective factor for diabetes are consistent with an earlier study by Fagot-Campagna et al. (2) of 787 Pima Indians aged 15 years or older. Because of a high incidence of diabetes (76 men and 185 women developed diabetes during 10 years), the Pima study had greater power to find a relation between lipoproteins and diabetes. Similar to the Finnmark finding (1), HDL cholesterol was inversely related to diabetes incidence among Pima Indian women but not men, when controlled for age, body mass index, systolic blood pressure, and 2-hour glucose. In both studies, there was no effect of lipids other than HDL cholesterol on diabetes incidence when controlled for potential confounders. Replication of results in two very different populations is always interesting, and we would like to comment further on these results.

Whether HDL cholesterol is directly involved in the development of type 2 diabetes is not clear. HDL cholesterol could simply be a marker for another explanatory factor, or it may act as an intermediary between a third factor and diabetes. Pima Indians were more obese, had lower HDL cholesterol levels, and were probably more insulin resistant than the Norwegians. Insulin resistance, an established risk factor for diabetes, might underlie the relation between HDL cholesterol and diabetes. Specific measures of insulin resistance were not available in the Finnmark study (1). However, Fagot-Campagna et al. (2) accounted for estimated insulin resistance, and HDL cholesterol remained protective of diabetes among Pima Indian women. Alcohol consumption and physical activity increase HDL cholesterol levels and may confound the relation between HDL cholesterol and diabetes if they are associated with diabetes. Alcohol consumption and physical activity may also explain sex differences if they are distributed differently among men and women. However, both of these studies controlled for alcohol consumption, and Njølstad et al. (1) also controlled for physical activity. The observed difference in the HDL cholesterol effect between men and women may also be due to differences in HDL subfractions between the sexes, and the subfractions themselves may have differential associations with diabetes.

A high HDL cholesterol level may reflect sex hormone balance and could explain why, in both studies, a high HDL cholesterol level was a protective factor for diabetes among women only. Both studies reported that menopause had no significant effect on the relation between HDL cholesterol and diabetes. Interestingly, another study among American Indians showed that a high HDL cholesterol level was a protective factor for diabetic nephropathy among women only, and this effect was slightly stronger before menopause than after, suggesting a sex hormone effect (3).

Results replicated in two studies from diverse populations strongly suggest that a higher HDL cholesterol level is a protective factor for type 2 diabetes among women. Alcohol consumption, physical activity, or insulin resistance may partially account for this relation, but it appears likely that sex hormones may also be involved. As Njølstad et al. (1) pointed out, an interesting implication is that the attenuated sex differences in coronary diseases among diabetic subjects may be associated with sex-related differences in diabetes determinants. Further studies should explore this intriguing link between HDL cholesterol, HDL subfractions, and type 2 diabetes but should take into account a potential effect of sex hormones.

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