validity of Forman, *et al.*'s estimate of 3.5 mg of nitrite derived from nitrate in high risk areas (Table 7) where the prevalence of chronic atrophic gastritis is probably considerable. The estimate ignores firm evidence of nitrate reduction in the gastric cavity in subjects with atrophic gastritis.

A second question may be raised on the validity of estimating exposure of individuals to nitrate via measurements on nitrate in saliva. Studies in Colombia[10] published some years ago demonstrated a total lack of correlation between gastric cancer risk and salivary nitrate although there was a correlation with urinary nitrate. Eisenbrand *et al.*[11] reported exceptionally high values of nitrate and nitrite in a region in Iran which has a low rate of gastric cancer. They concluded from these data and subsequent studies in Germany that salivary flow may strongly influence salivary concentrations, such that "under cool climatic conditions . . . higher salivary flow rates will result in lower nitrite concentrations". Studies in our laboratory and others[12] have shown that salivary nitrate is not correlated with gastric nitrate, and that other ions, such as thiocyanate, may compete for the same anion transport system in salivary glands.

A third issue is the source of the nitrate. This was briefly mentioned, but underemphasized, in Forman *et al.*[1]. It is well-known that vegetables are an important source of nitrate, but it makes a big difference if the vegetable carrying nitrate is a starchy root tubercle or cereal grain, which correlate positively with gastric cancer risk[13], or green leafy vegetables and fresh fruits which correlate negatively with such risk. The carrier of the nitrate may overshadow the correlation with nitrate itself.

In balance, epidemiological studies have shown that some vegetables are protective even though they contain high quantities of nitrate. This could also be a conclusion of the article by Forman *et al.*[1]. And in fact, such a conclusion would put them in total agreement with the earlier literature.

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FORMAN *ET AL.* REPLY—Tannenbaum and Correa state that the general message of our paper "is the lack of an etiologic role for nitrite in gastric cancer". What in fact we stated was "our results in general weigh against the idea that environmental nitrates play a *major* role in determining the risk of gastric cancer in Britain. They should *not*, however, be taken to imply that nitrate-related N-nitroso-compound carcinogenesis has no role in the development of gastric tumours" (our new emphasis). In other words, we clearly accept that nitrates and nitrites may have an aetiological role but not the major role in the context of Britain.

Although the distinction may appear trivial, it carries critical implications and relates directly to the role of epidemiology in our understanding of cancer. We agreed with Tannenbaum and Correa in recognizing the limitations of epidemiological methods when dealing with sophisticated multicausal models of carcinogenesis such as they and their colleagues have advanced in the area of gastric cancer. It would of course be futile to expect epidemiology to provide a complete description of the role of nitrates and nitrites in a complex pathway of events that involves numerous other interacting variables. However if nitrate exposure is a *crucial* factor in the development of gastric cancer, epidemiologists can legitimately ask the question of whether populations that experience a lot of gastric cancer have a high nitrate exposure (as we did in our paper) or alternatively whether populations exposed to a lot of nitrate experience an excess of gastric cancer (as in our recent study of fertilizer workers, manuscript in preparation). A negative answer to such questions does not mean that nitrates have no role, only that they are not a rate limiting factor and cannot explain the geographic distribution of the disease.

One has therefore to look for additional factors that are associated with an increased risk of gastric cancer. These other factors may also be dietary in origin and may be responsible for the development of atrophic gastritis or they may be the nitrosatable substrates that will react with nitrite to form *N*-nitroso compounds. Our results would suggest that, if nitrates are involved in the production of carcinogenic *N*-nitroso compounds and hence the aetiology of gastric cancer, then even quite low levels of nitrate exposure may still be sufficient to have a detrimental effect. In this context it might be more practical to manipulate the other associated factors rather than attempt to reduce nitrate exposure from an already low level.

To put it another way, our estimate of 3.5 mg nitrite derived from nitrate in high risk populations may well be wrong, because of the higher prevalence of people with gastritis who whould have an increased capacity for the formation of nitrite in the stomach. However, it would seem likely to be more beneficial to ascertain why these populations develop gastritis rather than to cut down an existing low exogenous nitrate level.

Tannenbaum and Correa make two further technical points, both of which we addressed in our original paper. The first is whether salivary nitrate and nitrite are valid measures of exposure. Table 8 in our paper shows a quite clear relationship between intake of dietary nitrate, from all sources and salivary nitrate and nitrite. If, as recent work by Tannenbaum and colleagues has shown, gastric juice nitrate does not correlate with salivary nitrate this again means that some factor other than exogenous nitrate is critical in determining the eventual gastric juice concentration.

The other technical point concerns sources of nitrate and whether certain types of dietary nitrate are more harmful than others. Certainly salivary nitrate reflects a global nitrate exposure and can not tell one anything about individual sources. From our dietary analysis meat-associated nitrate and nitrite are correlated with a high cancer risk (unlike vegetable or drinking water nitrate) but this is a very small proportion of total nitrate exposure. However, it can be a substantial proportion of nitrite intake, and because preserved meat will also contain nitrosatable amines which would reach the stomach simultaneously with the nitrite, it might be a specific hazard although this is not suggested by the available epidemiological data. Certainly more analysis needs to be carried out on individual foods and food groups.

In sum we agree with Tannenbaum and Correa that epidemiology is not equipped to deal with the full complexity of carcinogenic processes. Laboratory analyses can result in specific hypotheses about specific compounds, but epidemiology is the only way of fully testing the importance of these hypotheses in human populations and hence lead to informed public debate about prevention.

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