Correspondence

Carcinogenicity of chromium and its salts

SIR,—In a recent editorial (1986;43:649-51) Norseth discussed the complex problem of chromium carcinogenicity. He presented some of the myriad data resulting from epidemiological investigations, animal carcinogenicity assays, short term tests, and biochemical studies. The emerging concept that some reactive intermediate formed during the intracellular reduction of hexavalent chromium—for example, the pentavalent form—may be the ultimate carcinogen was also presented. Also, we agree that the experimental data may perhaps reflect the involvement of multiple mechanisms in chromium toxicology.

We were disappointed, however to read Norseth's conclusion that "all chromium compounds must be regarded as having a carcinogenic effect." Such a statement is not substantiated by the bulk of available publications and, most important, does not take into account that chromium is an essential element. Therefore, we cannot share the view that all the forms of chromium, even those playing an "essential" nutritional part, may be regarded as carcinogenic.

In addition, we would like to contribute to the invitation that "further studies on the microkinetics of the various chromium compounds in different cell systems and in the respiratory tract of experimental animals seem to be urgently required." In fact, we have been investigating in short term tests a large number of chromium compounds of different valence, physical state, and solubility. Moreover, we have been exploring chromium metabolism using several tens of biological preparations, including body fluids and cell preparations of various tissues from different animal species, including man, either under normal conditions or under the influence of diseases, drugs, enzyme inducers, metabolic inhibitors, special diets, and treatments. We cannot summarise these data but we would like to complete some of the points raised in the editorial.

A fundamental issue is the site at which hexavalent chromium is reduced. Due to the poor ability of trivalent chromium to cross cell membranes, reduction outside target cells provides an important detoxification device. This occurs actively in erythrocytes, which may explain the delimitation of chromium carcinogenicity at administration sites. Saliva and gastric juice are also efficient in reducing chromium (several tens of milligrams a day in man, as assessed on the basis of circadian analyses) (De Flora S, *et al*, unpublished observations), thus presenting an almost insurmountable barrier to chro-

mium taken by mouth. Reduction is also achieved in the extracellular environment of the lower respiratory tract—the so called epithelial lining fluid—and inside pulmonary alveolar macrophages. These cells, in terms of specific activity, are even more efficient than liver cells and, interestingly, reduction is further stimulated in cigarette smokers.¹

Hexavalent chromium which avoids this defence tends to be reduced inside target cells by specific and inducible mechanisms.² Even in the cell, as emphasised by Norseth, the site of reduction is crucial in determining the bioavailability of chromium to target DNA molecules. We would like to add that the cytoplasmic reduction is not only microsomal and mitochondrial but chiefly cytosolic.³ An important activity involved is DT diaphorase,³ as we have recently confirmed by using the purified enzyme. Since DT diaphorase catalyses a two electron transfer from NADPH and NADH, in the case of chromium this mechanism would bypass formation of the highly reactive pentavalent form.

In conclusion, we think that chromium should not be regarded as "universal" carcinogen, because several mechanisms constitute a threshold limiting its bioavailability and attenuating its potential effects in vivo.

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References

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- 3 De Flora S, Morelli A, Basso C, Romano M, Serra D, De Flora S. Prominent role of DT-diaphorase as a cellular mechanism reducing chromium (VI) and reverting its mutagenicity. *Cancer Res* 1985;45:3188-96.

SIR,—In his editorial (1986;43:649-51) Norseth begins by claiming that "A metal cannot be classified as carcinogenic per se since its different compounds may have different potency." In this we wholeheartedly agree and suggest that most of the research over the past 30 years has attempted to distinguish between those chromium compounds that do not appear to present a carcinogenic risk to workers from those that do. Furthermore, this research has tried to identify