MONITORING OF HUMAN SUBJECTS FOR ENDOGENOUS CARCINOGEN FORMATION AND EXPOSURE
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Endogenous formation of N-nitroso compounds (NOC) from ingested precursors ($R\text{-}NH_2$, NO_3^-/NO_2^-) may be the largest single source of exposure to these compounds for the general population. We have developed a sensitive method (Cancer Res., 41, 3658-3662, 1981) for the quantitative estimation of endogenous nitrosation by measuring N-nitrosoproline (NPRO) excreted in the urine per 24 hrs. The application of this method has allowed us: (a) to study the kinetics and factors affecting the nitrosation *in vivo* in human subjects/animals after administration of proline and nitrosating agents, and (b) to implement clinical and field (pilot) studies in human subjects at high risk for stomach and oesophageal cancer and in appropriate controls. Data from these studies has been obtained indicating (a) the applicability of the NPRO method, and (b) large inter-individual and geographical variations in exposure to endogenous NOC.

TUMOUR CELL HETEROGENEITY: EFFECT OF IMMUNOTHERAPY ON DIFFERENT CELL SUBPOPULATIONS
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We have investigated the effect of specific and non-specific immunotherapy on the growth and spontaneous metastasis formation of tumour induced by different tumour cell subpopulations of a transplantable anaplastic carcinoma of the Y59 rat. Tumour was generated by 5×10^5 cells injected into foot-pad. Twenty two days thereafter tumour cell suspensions from the primary tumour and from metastatic lesions that arose in the tumour draining popliteal lymph node or in the lung were prepared. The procedure was repeated three times. Tumour cells of each preparation were injected into the foot-pad of syngeneic recipients which were normal or specifically immunized or treated with BCG and *C.parvum*, respectively. Tumour originating from the cell suspension of the primary tumour or from the lymph node metastasis grew faster than tumours from lung metastases. Tumours of lung metastasis origin however gave rise to many more metastases in the lung than other two. In the specifically immunized rats, the growth of tumours originating from foot-pad tumour or from lymph node metastasis was retarded; the number of spontaneous lung metastases was also significantly diminished. Tumours originating from the lung metastasis, although insensitive to specific immunological attack were very sensitive to the effects of the biological response modifier.

METABOLIC REDUCTION OF THE ENVIRONMENTAL POLLUTANT 1-NITROPYRENE TO A GENOTOXIC PRODUCT IN MAMMALIAN CELLS.
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A large percentage of the bacterial mutagenicity associated with diesel exhaust and urban air particulates has been attributed to 1-nitropyrene. Formation of a DNA adduct, N-(deoxyguanosin-8-yl)-1-aminopyrene, in bacteria treated with 1-nitropyrene suggests that nitroreduction may play a significant role in the metabolic activation of this nitrated polycyclic aromatic hydrocarbon. In the present study, we have investigated the genotoxicity and DNA adducts produced by treatment of mammalian cells with 1-nitropyrene. At concentrations of up to 60 μM, 1-nitropyrene was only marginally mutagenic at the HGPRT locus in cultured CHO-K1 cells. However, its reduced metabolite, 1-nitrosopyrene, produced a clear, dose-related mutagenic response, a decrease in cell survival, and afforded the same DNA adduct observed in the bacterial genome. In human diploid fibroblasts, 1-nitropyrene was reduced to a genotoxic product that caused transformation to a state of anchorage independent growth and cellular invasiveness. Analysis of the fibroblast DNA indicated the presence of N-(deoxyguanosin-8-yl)-1-aminopyrene. These data suggest that in mammalian cells 1-nitropyrene is reduced to reactive intermediates that are capable of inducing toxicity, mutations and transformation, and that the reduction of 1-nitrosopyrene may be the rate limiting step in this activation.