MEMBRANE-MEDIATED CHROMOSOMAL DAMAGE. P.A.Cerutti[1], I.Emerit[2] and R.Zimmerman[1]. [1]Department of Carcinogenesis, Swiss Institute for Experimental Cancer Research, CH-1066 Epalinges s/Lausanne, Switzerland, [2]Cytogénétique expérimentale, Institut Biomédical des Cordeliers, 15-21 Rue de l'Ecole de Médecine, Paris 6e, France.

Agents operating via indirect action produce secondary DNA damaging agents in reactions with cellular molecules other than DNA. The secondary agents are mostly active oxygen species, lipid-hydroperoxides and aldehydic compounds. Membrane-active agents can cause chromosomal damage by this mechanism. They induce an oxidative burst, stimulate the arachidonic acid (AA) cascade and facilitate the autoxidation of lipids by disturbing the conformational integrity of cellular membranes. Certain tumour promotors, complete carcinogens, hormones, growth factors and particulates belong to this class of agents.

This model of "membrane-mediated chromosomal damage" is supported by our work with the tumour promotor phorbol-myristate-acetate (PMA). PMA produces extensive chromosomal damage in human lymphocytes and induces the formation of a clastogenic factor (CF). Antioxidants and inhibitors of the oxidative metabolism of AA inhibit the clastogenic action of PMA and of PMA-induced CF. It follows that active oxygen and metabolites of AA are intermediates in the formation of chromosomal damage by PMA. Chromosomal damage induced by this mechanism may modulate the expression of genes which play a role in promotion such as ornithine decarboxylase (ODC). Indeed, the antioxidants superoxide dismutase (SOD), catalase and most efficiently the combination of the two enzymes suppressed the induction of ODC in mouse mammary tumour cells.

A direct indication for a promotional effect of active oxygen was obtained with the mouse embryo fibroblast $10T\frac{1}{2}$ *in vitro* transformation system. Cells were initiated either with x-rays or benzo(a)pyrene-diol-epoxide I at doses which resulted in little or no formation of malignant foci. When these cultures were treated daily for three weeks with xanthine oxidase/xanthine which produces an extracellular burst of superoxide radicals a strong enhancement of malignant transformation was observed. Simultaneous addition of SOD reduced this promotional effect. These results support the notion that tumour promotors such as PMA operate via indirect action, i.e. the intermediacy of active oxygen, lipid-hydroperoxides and their degradation products.

INTERACTION BETWEEN CHEMICAL AND VIRAL ONCOGENIC AGENTS: LONG AND SHORT TERM STUDIES L.Chieco-Bianchi[1], A.Aldovini[1], F.Ronchese[1], A.De Rossi[1], F.Majone[2] and A.G.Levis[2] [1]Laboratory of Oncology and [2]Laboratory of Cytology, Venetian Region Centre for Environmental Carcinogenesis, University of Padova, Padova, Italy.

To study the mechanisms of chemical-viral interaction in carcinogenesis a series of experiments have been performed using the BALB/Mo mice which carry the Moloney murine leukaemia virus (M-MuLV) as an endogenous virus. It has been found that: (1) the frequency of sister chromatid exchange (SCE) induced by chemical mutagens is higher in spleen lymphocytes from BALB/Mo than in those obtained from BALB/c (M-MuLV free) donors; (2) inhibitors of virus synthesis reduces to BALB/c values the frequency of SCE in BALB/Mo lymphocytes; and (3) urethane treatment at perinatal age accelerates lymphoma development in BALB/Mo mice but does not modify, in comparison with BALB/c mice, the incidence, number and latency of lung adenomas. These data support the view that slow transforming retroviruses act as insertional mutagens.

INDUCTION OF UNSCHEDULED DNA SYNTHESIS (UDS) BY URINARY METABOLITES OF CARCINOGENIC ARYLAMINES IN HUMAN UROTHELIAL CELLS. Britta Christensen and Ching Y.Wang. Fibiger Laboratory, Copenhagen, Denmark and Michigan Cancer Foundation, Detroit, Michigan, USA.

The acetylated and nonacetylated N-hydroxy derivatives of 2-aminofluorene (AF), 4-aminobiphenyl (ABP) and 2-aminonaphthalene (AN), the N-glucuronic acid conjugates of the hydroxylamines, and the O-glucuronic acid conjugate of N-OH-AAF were studied. UDS determination was according to the method described (Cancer Res., 42, 3974, 1982). N-OH-AF, N-OH-AAF and the N-glucuronide of N-OH-AF were active in human urothelial cell lines HCV 29, 1752, and 1734, but the O-glucuronide was not. N-OH-ABP, N-OH-AABP, N-OH-AN, N-OH-AAN, and the N-glucuronide of N-OH-ABP were active in HCV 29. However the N-glucuronide of N-OH-AN was not active. When tested in a primary culture of human urothelial cells, N-OH-AF, N-OH-AAF, N-OH-ABP and N-OH-AABP were active, but N-OH-AN and N-OH-AAN were not. These results are in agreement with the UDS studies in rat hepatocytes and urothelial cells that have shown to be insensitive to AN, and demonstrate that human urothelial cells are able to activate N-OH-N-acetyl metabolites of carcinogenic arylamines. The relative insensitivity of rapid acetylators in comparison with slow acetylators in human population to the bladder carcinogenesis by arylamines appears to be due to the detoxification of hydroxamic acids by the O-glucuronidation that takes place in the liver. (Supported by USPHS Grant CA 23800).