GENOME INSTABILITY AND DNA REPAIR DEFICIENCY SYNDROMES - LINKS WITH CANCER
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The study of cells from human syndromes showing mutagen-sensitivity or cancer-proneness is throwing light on the ways in which human cells respond to DNA damage. Originally the sun-sensitive syndrome xeroderma pigmentosum was taken to support the somatic mutation theory of cancer since the deficiency in excision repair resulted in both a high incidence of light induced skin cancer and a high frequency of UV-induced gene mutations in cell culture. However, other syndromes (eg Cockayne's) showing the latter without the former or (eg some familial melanoma individuals) the former without the latter show that a simplistic interpretation is unwarranted. Other diseases, eg ataxia-telangiectasia, indicate the importance of immune deficiency in DNA repair-deficient individuals and some results will be described from an agammaglobulinaemia patient whose cells appear to be deficient in a DNA ligase function.

SYNERGISTIC INTERACTION OF TETRADECANOYL-PHORBOL ACETATE AND MURINE GRANULOCYTE-MACROPHAGE COLONY-STIMULATING ACTIVITY IN VITRO.
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Addition of tumour-promoting phorbol esters to haemopoietic cell cultures results in increased clonal proliferation. We examined two mechanisms by which tetradecanoyl-phorbol-acetate (TPA) might induce granulocyte-macrophage (GM) colony formation: indirect interaction of TPA with GM progenitors via modulation of growth factor production by stromal fibroblasts, and TPA alteration of GM progenitor cell sensitivity to colony-stimulating activity (CSA). Firstly, we tested the ability of TPA to modulate CSA, colony-inhibiting activity (CIA), prostacyclin I_2 (PGI_2) and prostaglandin E_2 (PGE_2) production by an in vitro representative of the haemopoietic stromal microenvironment, the K347 bone marrow-derived fibroblast cell line. Although both PGI_2 and PGE_2 production was increased there was no change in CIA, which has previously been demonstrated to be a prostaglandin-like activity, or in CSA production. Secondly, we examined the ability of TPA to enhance GM colony formation in the absence of CSA. We found that TPA does not enhance GM colony formation unless there is a source of CSA in the culture medium. Our observations permit the conclusion that TPA alters the responsiveness of GM progenitors to CSA. The hypothesis that tumour-promoting phorbol esters render cells more sensitive to growth factors suggests a basis for tumour promotion in vivo.

MUTAGENIC EFFECTS OF CARCINOGENS IN MAMMALIAN CELLS
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The working hypothesis that tumour initiation by chemicals involved reaction with cellular DNA led to the study of mutation based tests for carcinogens. Although the potential of bacterial assays have been clearly established they have limited value for detailed mechanistic studies. For such studies, particularly with polycyclic hydrocarbons, mutation at the HPRT locus of V79 Chinese hamster cells showed a very close correlation with carcinogenicity even for stereoisomers. In contrast cell toxicity which was directly related to the total extent of DNA reaction, did not correlate with carcinogenicity. Analysis for HPRT enzyme activity, and two dimensional gel electrophoretic studies using antiserum to purified HPRT, suggested that many such mutants had arisen by single base changes within the gene for HPRT. Furthermore reversion studies of $HPRT^-$, CRM^- mutants, which could not be studied by the above methods, were consistent with this conclusion. Evidence of non-sense mutations and their reversion by suppression has been obtained. The availability of a cloned HPRT c-DNA probe has allowed further analysis of both revertible and non-revertible mutants.