more than 1100 locations all over Finland. Cancer incidence rates dating back to the year 1953 were produced by municipalities (mean population 10,000). As a first step both geochemical data and cancer incidence data were illustrated as maps showing the areas with high and low concentrations and rates in 10-colour scale. On the basis of the hypotheses generated by visual observation of the maps or those known from the literature, a statistical multivariate analysis will be conducted by taking into account the known associations discovered in earlier analyses by the Finnish Cancer Registry between different background variables characterizing the municipalities (industrial structure, social welfare, living conditions, latitude, etc.), and individual cancer forms.

DNA-PROTEIN CROSS-LINKING BY CYTOTOXIC DRUGS

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Analysis of DNA and DNA-protein by buoyant density centrifugation and electrophoresis of fractions revealed that exposure of SV40 transformed mouse BALB/c fibroblasts to the alkylating agent nitrogen mustard reduced the amount of DNA that banded in an isopycnic caesium chloride (CsCl) gradient and resulted in a greater proportion of DNA sedimenting at lower densities. Analysis of the drug treated and untreated DNA purified from the CsCl gradient revealed trace amounts of protein of molecular weight 20 to 25K (detected by silver staining) associated with the nitrogen mustard treated DNA.

These findings were correlated with cytotoxicity (as assayed by colony-formation assays and radiolabelled thymidine incorporation into DNA) and the studies are being extended to novel platinum-containing agents.

SEARCHING FOR NEW ONCOGENES AT THE JUNCTIONS OF TUMOUR SPECIFIC CHROMOSOMAL ABNORMALITIES

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Chromosomal abnormalities which appear to be tumour specific may be involved in aetiology of the malignant cells. Abnormalities involving chromosome bands 14q11 and 14q32 are frequently observed in human tumours as rearranging genes (T cell receptor α chain and immunoglobulin heavy chain genes respectively) exist at these positions; this appears to enhance these interchromosomal exchanges. We have examined a number of different abnormalities involving 14q11 or q32 in an attempt to define new oncogenes by their occurrence at the junction of the abnormality and by the ability to detect mRNA transcripts from these genes. The nature of such transcripts has been investigated.

INTRACEREBRALLY IMPLANTED MAMMARY CARCINOMA CURED WITH ACETAMIDO-CNU AND HECNU

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A mouse mammary carcinoma (MCa) implanted intraperitoneally (i.p.), intravenously and intramuscularly can be cured with acetamido-CNU and hydroxyethyl-chloroethyl-nitrosourea (HECNU) (Radacic et al, Chemoterapia 2: 455, 1983). Further, we have studied the sensitivity of intracerebrally implanted MCa to those drugs. Animals were inoculated with different numbers of tumour cells ranging from 10^6 to 10^3 given in 0.05 ml (in one group, 0.1 ml). One day later, animals were treated i.p. with acetamido-CNU (15 mg/kg) or HECNU (20 mg/kg). The efficacy of the drugs was higher when the tumour cell inoculum was 0.05 ml than with 0.1 ml. Antitumour effects of acetamido-CNU were higher than the antitumour effects of HECNU. One-third of the animals inoculated with 10^5 tumour cells and treated with acetamido-CNU were cured, and all animals inoculated with 10^4 or 10^3 cells were cured. HECNU-treated animals were cured only when the inoculum was 10^3 cells or less.

TAQ I POLYMORPHIC ALLELES OF H-ras-1 PROTO-ONCOGENE PREFERENTIALLY ASSOCIATED WITH MALIGNANT MELANOMA

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A polymorphism based on a variable number of repetitions in a region (VTR) of the human H-ras-1 proto-oncogene has been reported and used to define different classes of alleles that were designated as "common" and "rare". The latter have been found to be significantly associated with

susceptibility to cancer by Krontiris et al (Nature, 313: 6369, 1985). We studied the DNA from normal leukocytes of a group of fifty melanoma patients and of fifty healthy individuals and failed to find any significant association between melanoma and rare alleles defined by MspI/HpaII digestion. We have recently described a new polymorphism in the VTR region of H-ras-1 based on the presence of additional TaqI restriction sites (Pierotti et al, Nucleic Acid Research, 14: 4379, 1986). Digesting our DNA samples with TaqI, we observed that the frequency of the allelic variant containing TaqI restriction sites within the VTR region was three fold higher in melanoma patients than in unaffected individuals.

EXPRESSION OF THE c-Ha-ras GENE IN DMBA-INDUCED RAT MAMMARY TUMOURS TREATED WITH A NOVEL ANTIESTROGEN COMPOUND TOREMIFENE

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Rat mammary tumours were induced by DMBA in 8 week-old female Sprague-Dawley rats. The tumours were allowed to develop for approximately 8 weeks whereafter toremifene treatment (15 mg/kg daily) was initiated. Control rats were exposed similarly to DMBA but did not receive toremifene. Total RNA was isolated from 6 control tumours, 8 hormone-independent, and 10 hormone-dependent tumours. Total RNA was also isolated from the liver and uterus of control rats. The expression of c-Ha-ras gene was studied by Northern blot analysis using BS-9 probe (a clone specific for rat Ha-ras oncogene). The following conclusions were made: (1)The amount of Ha-rasmRNA did not differ significantly between the control group and the tumours insensitive to toremifene treatment. (2)In hormone sensitive tumours the expression of Ha-ras was reduced by approximately 40% when compared to the two other groups. (3)The amount of Ha-ras mRNA in liver was of the same order to magnitude as that in hormone dependent tumours whereas in the uterus the expression was somewhat lower.

NUCLEAR UPTAKE OF NGF, EGF, PDGF AND INSULIN, BINDING TO CHROMATIN RECEPTORS IN TUMOUR CELL LINES

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The mechanism of action of growth factors is unclear,although interaction with the surface receptors and internalization are generally accepted. We have found that NGF, EGF, PDGF and insulin, taken up by cells bearing appropriate surface receptors, are tightly and specifically bound to chromatin. All growth factors tested have been isolated from chromatin as non-degraded. Binding of growth factors to the isolated chromatin has been inhibited by MAbs directed against the surface receptor. NGF chromatin receptor has been immunoprecipitated by MAb 20.4 from Eco RI-digested chromatin of melanoma HS 294 (230 kd), proliferating in the presence of TPA melanocytes (230 kD) and colorectal SW 707 cells (35 kd).

MAb 425, anti-EGF receptor has been taken up and incorporated into the chromatin of A 431, SW 948 and WI 38 cells, while another MAb, Br 15-6A only in SW 948 cells. Chromatin binding of anti-EGF receptor antibodies seems to explain an agonistic or antagonistic effect on growth factors of some antibodies through direct action on gene regulation. We suggest that chromatin receptors for growth factors may be of special importance for intracellular activation of autonomic growth of tumour cells.

A 3T3-CELL DERIVED FACTOR TRIGGERS THE RELEASE OF A SELF MITOGEN FROM FcγRECEPTOR EXPRESSING T CELLS

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We tested the possibility of a proliferative response of Fcγ receptor (FcγR) expressing T cells to signal emitted by precancerous or cancerous non-lymphoid cells, as an attempt to explain the observed increase in the number of FcγR T suppressor cells in cancer patients. Hypotonic cell extracts derived from H-ras transformed and non-transformed NIH 3T3 cells, triggered a mitogenic response of FcγR positive T2D4 hybridoma T cells, originating from density arrested cultures. Kinetic studies indicated that the 3T3 cell derived factor (3T3-F) triggers the release of a self autocrine growth factor from the T2D4 target cells. While 60 to 120 min were required for a proliferative response to T2D4 cells to the signal emitted by 3T3-F, supernatants