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SOME POSSIBILITIES OF PREDICTING INDIVIDUAL CANCER RISK.

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Our studies indicate, that individual susceptibility to carcinogens can depend on peculiarities of their endogenous formation and metabolism, DNA injury and repair. In rats exposed to benzo(a)pyrene (BP) individual levels of urinary excretion of its activation product, BP-7,8-diol, positively correlated with tumour latency. Healthy smokers excreted with urine more BP-7,8-diol, than smoking lung cancer patients, but the latter formed higher levels of BP-DNA adducts thereby confirming the existence of cancer-prone metabolic phenotype. N-ethyl-N'-nitro-N-nitrosoguanidine earlier induced gastric cancer in monkeys (macaca fascicularis) with low activities of O^6-alkylguanine-DNA alkyltransferase in stomach mucosa. Nitrosation capacity of gastric juice in adults with gastritis was much higher, than in children with similar pathology. This can be accounted for higher susceptibility of children to N-nitroso compounds. In conclusion, an implication of these biomarkers can be helpful for predicting individual cancer risk.

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ANTICANCER AGENTS OF SIMILAR CHEMICAL STRUCTURE SHOW DIFFERENT MUTAGENIC ACTIVITIES

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Homo-aza-steroidal lactams have been used as biological platforms for the transportation of alkylating agents to the tumor site. Substituted aniline mustards esterified with such a lactam showed anticancer activity against various experimental tumors in mice. In this work, the mutagenic activity of 3 different esters of this lactam with bis(2-chloroethyl)aminophenoxyacetic acid and bis(2-chloroethyl)aminocinnamic acid, as well as the substituted aniline mustards and the lactam alone, were studied in the Salmonella/microsome assay. Although closely related in structure, these anticancer agents exhibited a broad spectrum of mutagenic activity from non-mutagenic (the lactam and one of the esters) to highly mutagenic (induction of his revertants 3 times over the control). These results support the statement that similarities in chemical structure do not necessarily imply similar biological activity.

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EFFECT OF SALT ON CARCINOGEN PENETRATION TO PROLIFERATIVE CELLS IN THE RAT GASTRIC MUCOSA

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Salt has a role as an etiologic agent in human gastric carcinogenesis, and enhances initiation and promotion of experimental gastric carcinogenesis. We have studied the penetration of N-(^{3}H)methyl-N'-nitro-N-nitrosoguanidine (^{3}H-MNNG), from the gastric lumen to proliferative cells in the gastric mucosa of Wistar rats after hypertonic salt damage. In microscopic sections prepared by immunohistochemistry and autoradiography the percentage of S-phase cells (bromodeoxyuridine labeled cells) labeled with ^{3}H-MNNG was registered. Double-labeled cells represent the cell population at risk of MNNG-induced carcinogenesis. In the antrum the mean percent of double-labeled cells was 9.5 before salt exposure and 1.2, 10.4, 29.7, and 18.9 at 10 min, 2 hr, 12 hr and 24 hr after damage. In the corpus the mean percent of double-labeled cells was 2.8 before salt exposure and 0.5, 4.1, 11.2, and 3.76 at 10 min, 2 hr, 12 hr and 24 hr after damage. Our results show that penetration of a carcinogen to proliferative cells in the gastric mucosa is inhibited in acutely damaged antrum mucosa, but facilitated during restitution 12-24 hr after damage.

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MONOAMINES STIMULATIONES IN EXPERIMENTAL CARCINOGENESIS

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Fact about role of CNS monoamines in cancerogenesis have been accumulated for a number years. The present investigation was designed to investigate the effect of interaction between a psychoactive drug (Piracetam) and other treatment modalities on survival time of tumor - bearing rats.

138 Wistar rats were used in the experiment. The animals were injected 1% 3-Methicholantren suspension in 10% Tylose, sc. under the dorsal skin of the neck in doses of 3mg/animal. Within 4-9 months, after a single injection, the rats developed tumors, at the site of injection. The surgical removal was performed when tumors reached size of 1-3cm. After surgical extirpation of tumors different groups of animals were treated by cyclophosphamide (sc. single dose of 50mg/kg for female and 100mg/kg for male) or by a psychoactive drug (Piracetam) administrated by GE tube 5 times/week; 100mg/kg. Autopsy and histological examinations were performed in all animals.

81,2% of animals from the group B (Piracetam, after the surgical removal of tumors) survived over 120 days versus 66,8% from the group C (Cyclophosphamide, after the surgical removal of tumors) and 50% of the group A (only surgical removal of tumors). In the group B the incidence of metastases is the least (87,1% of animals were without metastases), compared with group C (45,4% of animals were without metastases) and group A (27,3% of animals were without metastases). The difference are statistically significant.

The mechanism of antineoplastic effect Piracetam included the interaction of influences both on metabolism of Central Nervous System and tumor. Most probably, the neurotransmitters modulation exerted their influence on carcinogenesis not only regulation/disregulation of brain homeostasis, but also via direct effect on intracellular processes during cell development and differentiation.

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THE ROLE OF GENE IMPRINTING IN HUMAN TUMORIGENESIS: DEVELOPMENT OF A MODEL FOR TARGETED GENOMIC INVESTIGATIONS.

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The association between aberrations of the human genome and the development of cancer is well established. Gene imprinting, defined as gene expression based on the gamete of origin, has previously been implicated to be involved in tumorigenesis by the loss of tumor suppressor gene regulation and of imprinted proto-oncogenes and growth factors. Given the high level of synteny between the human and mouse genome, and the fact that the murine model can be easily adapted to gene imprinting studies via transgenic and chimeric methods, we undertook a project which correlated known murine imprinted data with established information of genomic sites reported to be involved in human tumorigenesis. A worldwide review of imprinting studies in the mouse was carried out. These extracted data were compared to synthenic regions on the human genome, identified through the Human Genome Project. Similarly, published data on chromosomal abberations associated with human cancer were identified and cross referenced to the above information. The final outcome of these investigations resulted in the identification of human genomic areas (or specific genes) associated with cancer and likely to be imprinted. These data were tested for accuracy by examining genes where the relation between imprinting and cancer are known (Wilms tumor, rabdomyosarcoma, chronic myeloid leukemia). Additionally, direction of parental expression of already established imprinted genes in the human were conserved in relationship to mouse synthenic genes. These data provide a powerful tool for directed studies of the gene imprinting process as it relates to human cancer. It also adds further support to the increasing recognition of genomic imprinting as a fundamental mechanism for tumorigenesis.

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EVIDENCE OF DNA OF HSV (I+II), HHV6 AND CMV IN THE MUCOUS MEMBRANE OF BRONCHIAL CARCINOMA, PLEURAMESOTHELIOMA, MORBUS BOECK AND BRONCHIAL ASTHMA

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Subject Investigated:
Since earlier studies of ours had found evidence of EBV- and HSV DNA in various types of tumors (germ-cell and colorectal tumors), the question arose whether these potentially oncogenic viruses would also appear in bronchial carcinoma, pleuramesothelioma, Morbus Boeck, and in the mucous membrane of patients with bronchial asthma.
Materials and Methods:
Specimens were gained from 25 patients. Nine of the patients had bronchial carcinoma of varying histology; 2 further cases involved pleuramesothelioma; 12 involved sarcoidosis; 2 patients manifested bronchial asthma; and also examined were mucous membrane specimens from 7 healthy persons. In-situ hybridization was conducted as per Brigatti. Via avidin-biotin-peroxidase using 3-amino-9-ethylcarbazole as the chromagen, evidence of covalent biotin-marked BAM HIV fragments of HSV (I+II)-, HHV6- and CMV DNA was found.
Results:
In the mucous membranes of 6/9 bronchial carcinomas, 1/2 of pleuramesotheliomas, 1/12 sarcoidosis cases, and in the two bronchial asthma patients, the tumor-cell nuclei, as well as the lymphocpithelial cells of the sarcoidosis, HSV (I+II) DNA was detected. In the healthy persons' bronchial mucous membrane specimens, however, there was no evidence of HSV (I+II) DNA. In 6/9 bronchial carcinoma cases, in 2/2 pleuramesothelial instances, in 3/12 sarcoidosis patients, we detected HHV6 DNA in the tumor-cell nuclei, as well as in the lymphoepithelial cells of the Morbus Boeck cases. In the 7 healthy mucous membrane specimens, no trace of HHV6 DNA was found. In 8/9 bronchial carcinomas, in 6/12 Morbus Boeck specimens, as well as in 1 mucous membrane specimen of a patient with bronchial asthma, we found evidence of CMV DNA in the tumor cells or in the lymphoepithelial cells. In none of the 7 healthy bronchial mucous membrane specimens was there evidence of CMV DNA.
Discussion:
The evidence of HSV (I+II)-, HHV6- and CMV DNA in the mucous membranes of patients with bronchial carcinoma of varying histology, or with pleuramesothelioma, sar-coidosis or bronchial asthma may indicate a viral agent behind these diseases. Since HSV (I+II), HHV6 and CMV can be involved in the transformation of healthy cells into malignant ones, the question arises as to the role of these viruses in the genesis of bronchial carcinoma, pleuramesothelioma, and bronchial asthma, and as to their involvement in the formation of granuloma in sarcoidosis. If this viral phenomenon does turn out to be an etiopathogenetic factor or a co-factor, it will have a far-reaching impact on therapy.
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