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3. E T MOLECULAR BIOLOGY OF ETHIONINE CARCINOGENESIS

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Some substances with confirmed carcinogenic activity do not react in the Ames test for carcinogenesis, i.e., they do not react with DNA. Among these is ethionine which does not react with DNA, but does react with transfer RNA. The latter reaction is specific for a minor species of tRNA, tRNA^{Lys}. This selectivity implies the intervention of some enzymes which recognize tRNA^{Lys}. In addition, we have discovered that administration of ethionine elevates progesterone levels in the target animal. The elevation is extraordinarily high, it can be as high as tenfold in addition to ethionine, two other carcinogens which are negative in the Ames test, actinomycin D and thioacetamide also elevate progesterone levels. The aim of this research project is to study the molecular mechanisms of this novel mechanism of carcinogenesis.

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1.0219. J PEDERIN SYNTHESIS VIA A CHIRAL PRECURSOR

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Pederin is the toxic compound found in the haemolymph of the staphylinid beetle, *Pederus fuscipennis*. Its structure and stereochemistry were established. With its multiple functionality and nine chiral centers, it is by far the most complex (nonprotein) defensive substance to be isolated from an insect source. Aside from its vesicatory activity, pederin inhibits tumor growth (induced chemically in *Lupinus albus* and with Sarcoma 180 in the mouse). Cultures of HeLa cells show almost complete disappearance of mitosis as well as other effects on exposure to solutions containing only 1 nanogram/ml of pederin. Biochemical studies indicate that pederin exerts its cytotoxic effects by blocking protein synthesis and DNA synthesis. In this role it is 1000 to 10,000 times more active than the common antimetabolites. Pederin has also been shown to induce cell fusion in human skin fibroblasts.

This project aims at the synthesis of pederin starting from a readily available chiral precursor, D-mannitol. The projected synthesis has as an especially attractive feature the direct introduction of one chiral center (which would otherwise be very difficult to control) with the correct absolute stereochemistry. Model experiments which have already been carried out have been encouraging. We plan to prepare optically active pederin and pederin analogs for biological, biochemical, and possible medical experiments. SUPPORTED BY U.S. Dept. of Health Education & Welfare, Public Health Service, National Inst. of Health, National Cancer Inst. \$21,180

1.0220. G U HYPERTHERMIA AND RADIATION INDUCED GENETIC DAMAGE

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The purpose of this research is an attempt to understand how hyperthermia sensitizes radiation induced damage. Mutagen sensitive strains of *Drosophila melanogaster* are subjected to hyperthermia treatment, 38°C for 1 hour, and then exposed to X-rays or gamma radiation. The strains are mutagen sensitive due to interference with some aspect of repair. A strain does not respond to hyperthermia effect radiation? The mutant may already have inhibited

the repair similar to what hyperthermia would affect. The hyperthermia has been shown in our earlier investigation to increase radiation induced, dominant lethal, recessive sex-linked and the loss of the X and Y chromosome in those broods which represent cells in spermatogenesis in or about meiosis. We have obtained information that hyperthermia enhances gross deletions of the X-chromosome. This and the above listed genetic aberrations will be investigated in 10 different mutagen sensitive stocks with respect to hyperthermia and radiation induced damage.

BIBLIOGRAPHIC REFERENCES: Sidney Mitter. Hyperthermia and Radiation Induced Genetic Aberrations. Mutation Research 59:123-128, 1979. SUPPORTED BY U.S. Dept. of Health Education & Welfare, Public Health Service, National Inst. of Health, National Cancer Inst. \$31,572

2.0221. H T W CAROTENOIDS AS ANTITUMOR AGENTS FOR SKIN TUMORS

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Light, particularly the sunburn spectrum (UVB, 280-320nm), has been implicated as an etiologic agent in the induction of skin tumors in animals and man. We have shown that the administration of carotenoid pigments to patients with erythropoietic protoporphyria can ameliorate the light sensitivity associated with this disease, and that the administration of these pigments to normal volunteers was found to have slight but statistically significant effects in delaying the appearance of erythema caused by the sunburn range. We have also found that phytoene, a precursor pigment having absorption maxima in the sunburn range, significantly decreased the epidermal reaction in guinea pigs exposed to this radiation. In addition, we and others have shown that carotenoid pigments can inhibit the formation of free radicals which have been implicated in photocarcinogenesis. Therefore, we propose to study the effect of the systemic administration of beta-carotene, phytoene, and other carotenoid pigments on the development of skin tumors induced by sunburn radiation and topical carcinogens in hairless mice.

We have established dosage levels and routes of administration which lead to significant accumulation of beta-carotene and phytoene in the skin of hairless mice, with no apparent toxicity. Methods already well-documented in the literature for the induction of skin tumors by sunburn radiation and topical carcinogen application will be used. Groups of hairless mice will be given carotenoids and appropriate placebos, and blood and skin levels of the pigments will be allowed to reach saturating levels before the tumor induction program begins. The mice will be observed for the development of skin changes and tumors. Tumors will be studied histologically and graded. Blood and skin carotenoid and vitamin A levels will be measured. The results of statistical analyses on the numbers of tumors and the time of tumor induction in the various groups of mice will indicate whether the systemic administration of carotenoids has any significant effect on tumor induction.

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2.0222. B L T U W DIOL EPOXIDE AND OTHER DERIVATIVES OF PAH AND AZA-PAH

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Increasing evidence that diol epoxides are important intermediates in the mutagenesis and carcinogenesis of polycyclic aromatic hydrocarbons has been amassed during the past year. Quantum chemical calculations which we applied to estimate the reactivity of diol epoxides have proven successful in correctly predicting that bay region epoxides should be the most reactive for a given PAH, and have correctly predicted the relative reactivity of diol epoxides derived from different PAH. PAH ring-substituted with nitrogen (aza-PAH) are being increasingly recognized as significant environmental contaminants, but have received meager attention from the standpoint of determining the metabolites involved in the carcinogenesis of the compounds and their structure-activity relationships. An examination of the literature on benz(c)acridine derivatives suggests that diol epoxide and dihydrodiol intermediates analogous to those

involved in PAH carcinogenesis may well be involved. The dihydrodiol and diol epoxide derivatives of benz(c)acridine will be synthesized in the author's laboratory and will be tested for biological activity through the collaboration of D.M. Jenna, Laboratory of Bio-organic Chemistry, NIAMOD and A.H. Conney at Hoffmann-LaRoche. The biological testing will entail studies of the ability of the dihydrodiols to be metabolically activated by a cytochrome P-450 enzyme system to species mutagenic to mutant *Salmonella* strains as well as examination of the intrinsic mutagenicity of the diol epoxide and other derivatives of benz(c)acridine. Selected derivatives will be examined for carcinogenicity depending upon the mutagenicity results. The dihydrodiols and diol epoxides will be made available for metabolism studies. Additionally, dimethyl derivatives of benzo(a)pyrene will be synthesized to probe the importance of steric effects in the enzymatic epoxidation of double bonds in benzo rings of PAH and in the hydration of benzo ring tetrahydroepoxides with epoxide hydrazide. A new stereospecific synthesis has been designed to make available benzo ring diol epoxides that are very difficult to prepare by current methods and will be pursued.

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2.0223. B P Q T EPIDEMOLOGY OF BRAIN TUMORS

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A case-control study of 230 patients and 230 "best friend or closest neighbor" controls is proposed to evaluate risk indicators of primary brain tumors (specifically histologically-confirmed astrocytic tumors: astrocytoma, glioma, glioblastoma multiforme, medulloblastoma). Despite the fact that brain tumors are the primary source of cancer mortality in youth, that a variety of brain tumor risk factors have been suggested, and that experimental data exist linking brain tumor development to specific chemical carcinogens and oncogenic viruses, no large population, controlled study has been done to determine the risk factors of brain tumor. Through self-administered questionnaire and telephone interview, we propose to: 1. Determine the relationship between demographic characteristics and risk of glial tumors. 2. Evaluate the role of occupational and environmental exposures and risk. 3. Evaluate the role of trauma. 4. Evaluate the role of familial factors. 5. Evaluate the role of infection as a risk factor. Although this study is analytic in design, it is hypothesis-generating in nature. The unique availability of a patient population which includes 100 new astrocytoma patients per year and the active brain tumor research interests of the investigators have created a situation in which a valid study of the epidemiology of these tumors may be completed in an efficient and inexpensive manner.

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2.0224. B T BIOCHEMICAL STUDIES IN CHEMICAL CARCINOGENESIS

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This Program-Project encompasses a broad fundamental approach to the chemistry, biochemistry, and biology of tumor initiation, promotion, and progression by chemicals. The program includes major studies on the activation of chemical carcinogens, the interactions of ultimate carcinogens with cellular macromolecules, biochemical events associated with the promotion of initiated cells to the development of gross tumors, factors that affect the differentiation of cells and the progression and regression of neoplastic or preneoplastic cells, and the biological and biochemical diversity of preneoplastic and neoplastic lesions. The program includes investigations at the