99 THE TUMOR-INHIBITORY ACTIVITY OF 5-FLUOROMETHYL-2'-DEOXYURIDINE (F_3TDR). Charles Heidelberger and Sandra W. Anderson (McArdle Memorial Laboratory, University of Wisconsin, Madison, Wis.)

The above compound was synthesized in this laboratory (J. Am. Chem. Soc. 84, 3597, 1962). It is mutagenic to bacteriophage T4, is incorporated into its DNA (Gottschling and Heidelberger, J. Mol. Biol., in press), as well as DNA of mammalian cells, and its nucleotide inhibits thymidylate synthetase (Heidelberger, et al., Fed. Proc. 22, 532, 1963). We now report the activity of F_3TDR against several transplanted mouse tumors. The drug was given daily for 7 days, starting 1 day after implantation. F_3TDR significantly inhibits the growth of Sarcoma-180, the ratio of the volumes of the treated to control tumors (T/C) on the 12th day was 0.2 at 150 mg/kg x 7; but was considerably less effective than FUDR. Against L-1210 leukemia F_3TDR produced a T/C (survival) of 1.6 at doses from 100-250 mg/kg x 7, and is, in contrast to FUDR it is effective when given orally. F_3TDR inhibits the Ehrlich ascites carcinoma, but less so than FUDR. However, F_3TDR was considerably better than FUDR in inhibiting the growth of Adenocarcinoma 755, producing T/C values at 15 days of 0.05 at 200 mg/kg x 7 without toxicity; T/C value of 0.1 was produced by FUDR at 80 mg/kg x 7 but with excessive toxicity. Unlike FUDR, F_3TDR also has activity (T/C of 0.1 at 200 mg/kg x 7) when given orally. Cells resistant to FUDR are cross-resistant to F_3TDR.

100 COMPARATIVE CARCINOGENIC EFFECTS OF DIETHYLNITROSAMINE BY DIFFERENT ROUTES OF ADMINISTRATION TO SYRIAN HAMSTERS. Katherine McD. Herrold, National Cancer Institute, Bethesda, Maryland. (Introduced by K. C. Snell)

Previous experiments demonstrated that tumors of the trachea, bronchi, anterior and posterior regions of the nasal cavity and liver are induced in Syrian hamsters with diethylnitrosamine (DENA) administered either by intratracheal, intragastric or subcutaneous routes. The purpose of this experiment was to determine what the effect other routes of administration, including intraperitoneal, intradermal and skin painting, have on the carcinogenic action of DENA. The present study includes observations on three experimental groups of Syrian hamsters to which DEN was administered for periods of 4-7 months. Fewer hepatocellular carcinomas were induced by these routes as compared with the results of subcutaneous administration. The carcinogenic effect, by all three routes evaluated in the present study, was greatest on the trachea, bronchi and nasal cavity thus suggesting that the major pathway of excretion for this carcinogen (DENA) or its metabolite is via the respiratory system.

101 THE ACUTE HEPATOTOXIC EFFECTS OF METHOTREXATE (MTX) THERAPY. E. M. Marsh, V. Wong, E. S. Henderson, and R. Rubin (NCI and NIAMD, NIH, Bethesda, Md.) Introduced by Carl G. Baker.

Hepatic fibrosis has been noted in leukemic patients receiving antimetabolites. Abnormal liver function tests (LFT) have been noted in women receiving MTX for choriocarcinoma. Since MTX is widely used in both malignant and inflammatory diseases a systematic study of its hepatotoxic effects was made. Intravenous dosage schedules of 35-100 mg/m^2 weekly were studied. The patients' diagnoses included: acute leukemia and peripheral uveitis. Control and therapy LFT and liver biopsies were done. Control studies were normal in all cases. At 25 mg/m^2 twice weekly mean maximum SGOT, SGPT, and BSP retention values were 118 units, 203 units, and 11% respectively 4 weeks after the onset of therapy. During repeated 5 day MTX courses mean maximum SGOT, SGPT, LDH, and BSP retention values were 162 units, 405 units, 717 units, and 16% respectively. Abnormalities were more pronounced with each successive course. Between courses LFT returned towards normal. Alkaline phosphatase became slightly abnormal in a few instances while bilirubin, cholesterol, cephalin flocculation, thymol turbidity, prothrombin time, and serum proteins retained normal. All liver biopsies done revealed fatty metamorphosis and a portal inflammatory reaction. It is concluded that the acute toxic effects of MTX therapy include a characteristic hepatotoxicity. If the demonstrated hepatic damage proves irreversible, it will limit the use of MTX in nonmalignant diseases.

102 GENETIC ANALYSIS OF LIVER CATALASE ACTIVITY IN C57BL MICE. W.E.Heston and M.Rechcigl, Jr.(National Cancer Inst.,NIH,Bethesda,Maryland)

At this meeting last year we reported that the liver catalase activity of substrain C57BL/6 mice is approximately half that of substrain C57BL/He although the kidney catalase activity is the same in the two substrains. Hybridization studies have now shown that this difference is primarily due to a single gene pair with low liver catalase activity dominant over high. Reciprocal F_1 hybrids were alike in liver catalase and were like the low C57BL/6 parent substrain. F_2's showed a bimodal distribution that did not differ significantly from a 3:1 ratio of low to high. Groups resulting from backcrossing F_1's to C57BL/6 were consistently like the C57BL/6. Those resulting from backcrossing F_1's to C57BL/He were consistently bimodal in distribution not differing significantly from a 1:1 ratio of low to high. High segregants of the C57BL/He backcross when mated to C57BL/He produced only offspring with high activity whereas the low segregants of this backcross when mated to C57BL/He produced offspring approximately half of which had high activity and half had low. The parent substrains and the various hybrid groups did not differ in respect to kidney catalase activity. Males consistently had higher catalase activity than females, the difference being more pronounced in the kidney than in the liver. It appears that low liver catalase activity is the result of a dominant mutation the action of which is not in the direct synthesis of catalase but inhibits or suppresses the activity in the liver without affecting that of the kidney.