709 CLINICAL STUDIES OF INTERFERON THERAPY. William A. Carter, Gerasimos E. Panagos, Judith A. O'Malley, Arnold I. Freeman, Leon Stutzman, Donald Higby, Harold Douglass, Douglas Holyoke, and Rita F. Buffett. Roswell Park Memorial Institute, Buffalo, N.Y. 14263.

Our studies were designed to accomplish three objectives: (1) to determine the therapeutic activity and cellular targets of a double-stranded(ds) RNA interferon inducer, polyinosinic-polycytidylic acid ($rI_n \cdot rC_n$), in cancer patients with cytolytic viral infections; (2) to determine structural features of the interferon molecule, as induced by dsRNA therapy or endogenous viral infection, and the relationship of the structural form to the ultimate clinical course; and (3) to determine the clearance of performed leukocyte and fibroblast interferon, a first step in evaluation of exogenous interferon as an antitumor drug. Twenty-one patients with hematologic malignancies and documented viral illness were treated with $rI_n \cdot rC_n$. At doses of 3 mg/kg (or greater), a serum interferon response was noted within several hours and persisted for 72-90 hours; serum interferon was seldom detectable in untreated patients. With a new set of affinity probes of human interferon (which measure its hydrophobic "pockets" and glycoprotein nature), we also showed that dsRNA therapy induces 3 molecular forms of interferon: a fibroblast form, a leukocyte form, and a 3rd species, presumably derived from lymphocytes (the "immune" interferon?). These affinity probes have allowed us to purify interferon some 5,000-10,000 fold with full recoveries, and thus the purified preformed molecules can now be exogenously supplied.

710 NUCLEIC ACID INHIBITION AND THE CHEMOTHERAPEUTIC SYNERGISM OF ADRIAMYCIN(NSC 123127) AND CYCLOPHOSPHAMIDE (NSC 26271). S. McNitt, D.W. Yesair, J. Tobias and I. Wodinsky. Arthur D. Little, Inc., Cambridge, Ma. 02140 and St. Bartholomew's Hospital, London, England.

Adriamycin (A) and cyclophosphamide (C) resulted in greater chemotherapy than either drug alone against L1210 lymphocytic leukemia (Brit.J. Cancer 32:199,1975) and against P388 leukemia (IXth Intern. Congress Chemother.,July 1975, Abs.C-24). The effects of (A) 10 mg/kg and (C) 250 mg/kg on the incorporation of ^{3}H-thymidine (T) into nucleic acid fractions of bone marrow and ascites P388 cells were determined after i.p. administration of the drugs singly (5 days after 10^6 cell inoculation) and in combination [day 5 (A) and (C), day 5 (A), and day 8 (C)] to tumor-bearing mice. Each drug singly inhibited incorporation of (T) into nucleic acid fractions of bone marrow and tumor; the magnitude of this inhibition was smaller and the time to recover from inhibition was faster in bone marrow than tumor and the duration of this inhibition in both cell types was greater with (C) than with (A). When both drugs were given on day 5, the incorporation of (T) was similar to that for (C) alone. Administration of (C) 3 days after (A) prevented recovery of (T) incorporation in tumor to a greater extent than bone marrow. This inhibition by (C) of the recovery of (T) incorporation following (A) treatment, particularly in tumor, probably relates to the enhanced chemotherapy with this therapy schedule. Supported by Contract NO1-CM-53849 from DCT, NCI, NIH, DHEW.

711 COMPARATIVE DISPOSITION OF DICHLOROALLYL LAWSONE IN RATS BEARING WALKER 256 TUMOR AFTER I.V. AND P.O. ADMINISTRATION. M. Chadwick, D. Jaques and G. Berard. Arthur D. Little, Inc. Cambridge, Ma. 02140. (Introduced by I.Wodinsky).

Dichloroallyl lawsone (NSC 126771, DCL) was administered to rats at 34 mg/kg iv or po 6 days after tumor implantation im. Drug concentrations were determined by radiochemical and spectrophotometric technics. Total drug equivalent and DCL concentrations in plasma and heart were approximately 10 times higher at 2 min after DCL iv than po; also DCL equivalents were detectable in brain only at 2 min after DCL iv. These data correlate with DCL causing death by acute cardiac arrest and with 34 mg/kg iv being close to the maximum tolerated dose (MTD), whereas 34 mg/kg po is less than the MTD. Administration of DCL at 220 mg/kg po, which approximates the MTD, resulted in maximum DCL concentrations in plasma similar to those after 34 mg/kg iv. These data indicate that the toxic effects of DCL are related to achievement of a critical drug concentration at a receptor site. The areas under the concentration-time curves for DCL in plasma after iv or po administration were similar. The Cxt values for drug equivalents and, preliminary data indicate, for DCL itself in tumor and tissues such as heart and liver were also independent of the route of administration. These data correlate with the minimum effective dose of DCL being independent of the administration route, and indicate that the antitumor effects of DCL are related to the overall Cxt value of drug in plasma and tumor. Supported by Contract NO1-CM-53849 from DCT, NCI, NIH, DHEW.

712 MITOSIS OF MUSCLE SATELLITE CELLS DURING THE INDUCTION OF SKELETAL RHABDOMYOSARCOMAS WITH NICKEL SULFIDE. Carlo Bruni, University of Virginia, Charlottesville, Va 22903 (Introduced by Thelma B. Dunn)

The objective of this electron microscopic study was to determine the source of the stem cells of rhabdomyosarcomas induced in adult rats with a single injection (20 mg) of Ni_3S_2.

We reported (J.Nat.Cancer Inst. 34:687,'75) that the dividing cells of these tumors were undifferentiated and mononucleated, whereas the nondividing cells exhibited evidence of early differentiation and were, in part, multinucleated. In sum, the stem cells exhibited a characteristic morphology. Tumors result from proliferation that starts before they are recognized as macroscopic nodules. Thus the detection during the induction period of mitotic cells identical to the neoplastic stem cells might be taken to indicate that the dividing cells are the precursors of the tumors.

Cells in mitosis during the induction period were indistinguishable from the dividing cells in the tumors and exhibited all the features characteristic of the satellite cells, including a basement lamina continuous with that of the adjacent myofiber.

These and other findings indicate that rhabdomyosarcomas are derived from satellite cells, i.e. immature cells normally present in adult muscles, rather than from mononucleated cells resulting from the dedifferentiation and from the fragmentation of multinucleated myofibers. These findings, moreover, explain the undifferentiated features of rhabdomyosarcomas.