January

David H. Katz et al. (National Institutes of Health, Bethesda, Maryland and Harvard Medical School, Boston, Massachusetts) studied the effect of immunocompetent allogeneic lymphoid cells on a transplantable lymphatic leukemia (L2C) in guinea pigs. Animals of strain 13 were immunized with Freund’s adjuvant, and their lymph node and spleen cells injected into strain 2 guinea pigs prior to the inoculation of a lethal cell-dose of leukemia. The procedure was protective through a mechanism related to a graft-versus-host reaction.

A companion paper from the same group shows that guinea pigs with already existent leukemia treated by repeated allogeneic cell transfers had significant prolongation of survival. The potential therapeutic applications to man could be explored by the use of large numbers of peripheral donor lymphocytes. One obvious limitation might be the development of graft-versus-host manifestations.

Greater knowledge of the pharmacology of chemotherapeutic agents is usually useful in their more intelligent clinical use and toward improvements in the design of related agents.

Chun Jui Cheng et al. (Columbia University, New York, New York) investigated the interaction of CCNU [1-(2-chloloethy1)-3-cyclohexyl-1-nitrosourea] with nucleic acids and proteins in mice bearing L1210 leukemia, and on L1210 in vitro. CCNU was found to exert a dual capacity, of modifying proteins via cyclohexylcarbamoylation, and of nucleic acids via alkylation. The authors postulate that this dual activity may explain the broad cytotoxicity and activity of CCNU against tumors that are resistant to conventional alkylating agents. Clarification of its mode of action obviously will facilitate the search for related agents with similar reactivity that might have increased antineoplastic effects.

Engracio P. Cortes et al. (Roswell Park Institute, Buffalo, New York) concerned themselves with mithramycin, a cytotoxic antibiotic of clinical value in glioblastoma multiforme and testicular carcinoma. The compound was noted to lower the serum calcium. The investigators showed that mithramycin prevents the release of calcium by parathyroid extract from embryonic rat bone in vitro, at concentrations not lethal to the tissue. Thus mithramycin appears to inhibit bone resorption and this mechanism is proposed to explain its hypocalcemic effect.

D. M. Bissel and E. Alpert (Harvard Medical School, Boston) continue their interest in hepatoma and aflatoxin, by the report on cholesterol synthesis in patients from Uganda. Hepatic cholesterol synthesis is under the influence of a negative feedback by dietary cholesterol; this feedback mechanism is lost in primary hepatoma. In contrast with data from Boston, the high hepatoma-risk Ugandans included a number of patients without hepatoma who lacked the feedback inhibition mechanism. Also, the synthesis of hepatoma tissue was so low
that the presence of the feedback mechanism could not be assessed. The authors postulate that the first finding might reflect exposure to aflatoxin and thus indicate a biochemical "precancerous" lesion, and the latter might indicate greater dedifferentiation than is seen in the less common hepatomas in the United States.

Mikio Nishioka et al. (Yamaguchi University School of Medicine, Ube, Japan) localized α-fetoprotein in hepatoma tissue by immunofluorescence in 10 patients with primary hepatocellular carcinoma. It was found in the cytoplasm, cytoplasmic membrane and the perinuclear zone, in one fifth or less of the tumor cells. All but one patient had α-fetoprotein (AFP) in the serum. The presence of AFP, an embryo-specific α-globulin in serum is now of established clinical value for the diagnosis of primary liver carcinoma.

February

William D. DeWys (University of Rochester School of Medicine and Dentistry, Rochester, New York) presents an experimental model for the quantitative study of tumor response to chemotherapy. A transplantable lung carcinoma in C57B/6 mice, which metastasizes to the lungs and kidneys, is used. With cyclophosphamide, it was found that the more rapidly replicating cells were most sensitive. There was progressive slowing of the rate of growth as the tumor increased in size, in metastatic sites as well as at the inoculum primary. Immunologic factors were excluded by showing no evidence of resistance to repeated transplants. Removal of the primary reversed the decrease in the growth rate of metastases. The findings suggest some nonimmunologic systemic factors, such as tumor by-products, that influence tumor growth rate. It would be interesting to determine whether these effects can be observed with other transplantable isogeneic metastasizing tumors.

Robert A. Tobey (Los Alamos Scientific Laboratory, Los Alamos, New Mexico) describes a simple, rapid method for classifying chemical agents by their effects on the cell cycle. Using the synchronized CHO Chinese hamster cells in vitro, the agents are added during the G1 or S phase, and labeled and mitotic fractions determined in autoradiographs prepared with tritiated thymidine. It was possible to distinguish at least seven classes of compounds, including those inhibiting primarily the G1 to S transition, those affecting the initiation and completion of DNA synthesis and those affecting either G2-specific, mitotic or cycle-wide processes. These techniques, if they are validated and expanded, certainly will find a useful place in the search for cancer chemotherapeutic agents.

Charles Huggins and Hisao Oka (University of Chicago, Chicago, Illinois) find that hypophysectomy produced profound regression in 30 percent of rats with stem-cell erythroblastic leukemias induced by intravenous injections of a lipid emulsion of 7, 8-12-trimethylbenz(a)anthracene. There was prolongation of life as well as morphologic evidence of decreased peripheral leukocytosis and histologic invasion. This interesting observation certainly deserves early clinical exploration.

R. Douglas Thornes et al. (Royal College of Surgeons in Ireland, Dublin) report that daily infusions of Brinase (Protease 1 of Aspergillus Orzayae) in 6 patients with acute leukemia resulted in the production of complement-dependent autocytoxicity against leukemic cells and lymphocytes. The autocytoxicity is transient, lasting three to 15 days, but repeat courses of Brinase produce further autocytoxins. Remission was obtained in three of five patients given combination therapy and in one case of acute myeloblastic leukemia treated by Brinase alone.