Reporting on
Cancer Research

Commentary on the March and
April 1972 (Volume 32, Numbers
3 and 4) issues

Michael B. Shimkin, M.D.
Associate Editor

Experimental cancer chemotherapy is
alive and doing well on many major
fronts of research. It involves dis-
ciplines from molecular biology to
clinical medicine, and organisms from
microbes to man. The March and April
issues of Cancer Research contain a
variety of typical dispatches.

March
Tsu T. Chen and John Mealey, Jr.
(Indiana University Medical Center,
Indianapolis) examined the effects of
1-β-D-arabinofuranosylcytosine
(ara-C) on cultures of five human glial
tumor cell strains. Significant inhibition
was observed, and the cytotoxic effect
was enhanced by combination with 1,
3-bis(2-chloroethyl)1-nitrosourea
(BCNU). Obviously, in vivo studies
are required before the findings are
applied to the clinic, but in vitro systems
also have their place.

Gerald B. Grindey et al. (Roswell
Park Memorial Institute, Buffalo, New
York) compared the effects in vivo and
in vitro of combining 1-β-D-arabinofurano-
sylcytosine (ara-C) and 1-for-
myllisoquinoline thiosemicarbazone
(IQ-1). Therapeutic synergism occurred
in mice bearing leukemia L1210, where-
as in culture only additive effects were
elicted. The results indicate that the
therapeutic synergism in vivo was not
based upon direct interference with
cellular metabolism, but upon some en-
hancement of the host defenses, imm-
unologic or otherwise.

In another study, several inhibitors
of DNA synthesis were used on sus-
pensions of leukemia 1210 cells. Some
combinations showed antagonism,
others were additive and one was
slightly synergistic in this in vitro
system. The various interactions were
quite unpredictable, could not be
explained by present concepts concern-
ing combination chemotherapy and were
not the same as under in vivo conditions.

Fanny Lacour et al. (Institut Gustave-
Roussy, Villejuif, France) report that
treatment with double-stranded poly-
nucleotide complex, polyadenylic-
polyuridinic acid (poly A-poly U), re-
duced rate of tumor growth and in-
creased survival time in mice mastec-
tomized for spontaneous mammary
adenocarcinoma, and reduced the ap-
pearance of metastases in hamsters
bearing a transplantable melanoma. The
poly A-poly U is stated to be nontoxic,
and is postulated to exert its effect
through enhancement of immune me-
chanisms. It looks like a candidate for
adjuvant-therapy studies in man.

William A. Creasy et al. (Yale Uni-
versity School of Medicine, New
Haven, Connecticut) studied the
antineoplastic effect and metabolism of
2 α-(N)-heterocyclic carboxaldehyde
thiosemicarbazones in mice and in dogs
bearing spontaneous lymphosarcoma. A
high affinity for ribonucleoside diphos-
phate reductase and a slow rate of meta-
blolic transformation in order to main-
tain activity over longer periods were
found necessary for clinical activity. This class of chemicals is assuming an increasingly larger role clinically. The report is a demonstration of the usefulness of animals with spontaneous tumors in experimental cancer chemotherapy.

Charles B. Pratt et al. (St. Jude Children's Research Hospital, Memphis, Tennessee) summarize the results on 20 children with rhabdomyosarcoma who were treated by a systematized program of surgery, radiotherapy and chemotherapy with vincristine, cyclophosphamide and dactinomycin. Complete regression of tumor was achieved in 15, but only nine were alive two to 39 months later; of these, seven were clinically tumor free. These results are worthy of extension to more formal clinical trials, which should include appropriate parallel controls or contrast groups for comparison. As B. J. Kennedy and A. Theologides (Ann. Int. Med. 76: 321, 1972) recently again point out, the complex therapeutic combination approaches being reported for lymphomas and other neoplastic diseases "increases the responsibility of investigators to provide properly controlled studies."

April

Angelo Nicolin et al. (National Cancer Institute, Bethesda, Maryland) explored the antigenic properties of L1210 leukemia sublines which became drug resistant after prolonged in vivo treatment with different anticancer agents. Mice immunized with inactivated cells from 2 resistant sublines were protected against viable leukemic cells of the same sublines. Mice immunized with inactivated sensitive cells demonstrated considerably less protection. Cytotoxicity of serum of mice immunized with resistant subline cells was elicited to resistant subline cells but not to sensitive cells. These data indicate that new antigens were produced in drug-resistant variants of leukemia L1210.

Jeanne I. Rader and Dorris J. Hutchison (Sloan-Kettering Institute for Cancer Research, New York, New York) used a microbial model system as an aid in understanding drug-resistant variants. Completely defined media for microbes allow identification of resistance-associated changes that may be undetectable in less well-defined systems. The studies used streptococcus faecium strains from which were developed substrains resistant to two antifolates. Methasquin and amethopterin-resistant mutant strains were quantitatively and qualitatively different from the amethopterin-resistant strains. A number of mechanisms were described as contributing to resistance to the two antifolates.

Manley McGill and B. R. Brinkley (University of Texas M. D. Anderson Hospital and Tumor Institute at Houston) directed their attention to the mitosis of human normal and leukemic leukocytes during inhibition and recovery to colcemid, a potent inhibitor of mitosis in C-metaphase. The events were observed under light and electron microscopy, and described in detail. The recovery of chronic myelocytic leukemia cells from colcemid block proceeded at a rate much slower than normal leukocytes, and cells from one patient with acute myelocytic leukemia failed to recover. Leukemic cells thus appeared to be more sensitive to colcemid than normal cells. Ultrastructurally, the morphology of the centriole was most prominently atypical.