The March-April issue of Cancer Chemotherapy Reports contains a letter by Dr. Paul A. Bunn from the National Cancer Institute, Bethesda, Maryland, which raises a point with interesting implications. Dr. Bunn took issue with an article by Kovach et al. (Columbia University, New York, New York) previously published in CCR concerning a phase II study of cis-diamminedichloroplatinum in advanced carcinoma of the bowel. Kovach thought that while the drug had little value itself for the treatment of adenocarcinoma of the bowel, the drug should be used in trials with a combination of agents. Dr. Bunn questioned this recommendation. It is his feeling that if an agent is inactive when used alone, its use in combination trials should generally be unwarranted. At first glance, and perhaps beyond, it would seem that Dr. Bunn’s viewpoint is entirely defensible. However, many agents which are inactive with regard to a clinical antitumor effect have profound biochemical influences on normal and neoplastic tissue which may be demonstrated by antitumor activity in various murine screening systems. It is at least possible that compounds which are clinically inactive alone might provide surprises when used in combination with other agents. In the past, this approach has been clinically employed using compounds which influence known pharmacologic and biochemical pathways of primary anticancer agents. For example, allopurinol has been used in combination with 6-mercaptopurine, phenobarbital with cyclophosphamide, and various compounds inhibiting amino acid metabolism with L-asparaginase. Needless to say, the impact of such approaches pales to insignificance when compared to the effects of combining two or more active agents. Unfortunately (or fortunately, depending upon one’s point of view), the economics of current drug screening in murine systems demand that only active agents, and by that I mean agents which have proved active in the clinic, are looked at in drug combinations in screening systems. It is of course “mind-boggling” to conceive that agents which are inactive in the clinic, though active in animal systems, be also screened for unanticipated major therapeutic advantage when used in combination. It might prove too expensive, however, to put to the test Dr. Bunn’s viewpoint that inactive agents when used singly will offer little in combination with other active agents.

Two articles dealing with the terminal phase of chronic granulocytic leukemia, one by Levine et al., from the Southwest Cancer Chemotherapy Study Group, and another by Hayes et al., from the Acute Leukemia Group B, comment on the role of chemotherapy in what has come to be recognized as an extremely refractory disease. Levine comments that dibromomannitol was not therapeutically effective in either the blastic phase of chronic granulocytic leukemia or in chronic granulocytic leukemia which is resistant to busulfan.
Dibromomannitol is an interesting drug, a halogenated sugar alcohol which came to use in this country after some very encouraging early clinical and experimental work in Hungary. It is said to have the properties of both an alkylating agent and an antimetabolite. In the management of chronic granulocytic leukemia the drug produces approximately a 70-80 percent remission rate in nonresistant patients. It is not clear, however, that the drug is to be preferred over busulfan in such patients and there is some question whether busulfan will be effective in dibromomannitol-resistant patients. The article by Hayes comments that the blastic phase of chronic granulocytic leukemia can be defined and treated as a therapeutic entity. These criteria (for the blastic phase) may be of interest to CCR readers and include (a) peripheral blasts and promyelocytes greater than 30 percent, (b) the completion of two courses of conventional drug treatment and the discovery of one of the following: a hemoglobin of less than 92/100 ml. or a platelet count decreased below 100,000 platelets/mm³ from above that value during a conventional course of treatment, or (c) an increase of the white blood cell count after a conventional course of treatment to either 50,000 cells/mm³ or more than double the count at the start of the course of treatment. The therapy used by Hayes included both a high and a low dose weekly regimen with 6-mercaptopurine, a high and a low dose of 6-thioguanine and azaserine, a program of BCNU and cytosine arabinoside, and a final regimen including cytosine arabinoside, BCNU, vincristine, and prednisone. None of the treatments was sufficiently successful to warrant recommendation for general use. The authors note that the distinctness of this terminal phase of chronic myelocytic leukemia led to their belief that such patients constitute a useful group for clinical trial of new antileukemic agents.

Two studies comment on some unusual toxicities associated with the introduction of new experimental chemotherapeutic agents. Herman et al., writing from Microbiological Associates and the National Cancer Institute in Bethesda, Maryland, comment on the prevention of ellipticine-induced hemolysis in rhesus monkeys. Intravenous administration of ellipticine, which has considerable promise on the basis of preclinical screens, results in hypotension, bradycardia, and a brisk hemolytic syndrome within five minutes. The authors were able to prevent hemolysis by preparing the drug in citrate buffer or EDTA. It will be of some interest to follow whether such toxicity will occur if this drug is used in the treatment of man. The article illustrates the importance of preclinical pharmacologic testing of new agents prior to their introduction in the clinic. Krakoff et al., writing from the Sloan-Kettering Cancer Center, New York, New York, discuss a clinical trial with 5-hydroxypicolinaldehyde thiosemicarbazone. Although little in the way of encouraging clini-
cal anticancer activity was seen, the compound produced marked hemolysis, iron chelation, and urinary excretion of iron among its other more classic side effects. It is presumably the drug's binding with iron which accounts for many of its cytotoxic and antitumor effects, possibly by inhibiting ribonucleoside diphosphate reductase and other iron-containing proteins. The authors do not suggest additional work with the compound but comment that they are pursuing work with analogs of the thiosemicarbazone.

Another new agent which may prove to have more potential per se is the antitumor antibiotic carminomycin. This Russian antibiotic is similar to the previous anthracyclines, daunorubicin and adriamycin. One of the advantages of this new agent is that it is absorbed from the gastrointestinal tract and has exhibited activity in various preclinical tumor screens. It will be of interest whether studies will demonstrate a greater superiority in the clinic over its other anthracycline relatives. Gause et al. report this work from the Institute of New Antibiotics, USSR Academy of Medical Sciences in Moscow.

One of the more impressive combinations of drugs useful in disseminated testicular cancer is vinblastine and bleomycin. This drug combination is reported on by Spigel et al., of the Lackland Air Force Base in Texas, who comment that in 11 patients treated, five complete and four partial responders were observed. This program used bleomycin (.15 mg/m^2 twice weekly IV to a maximum total dose of 400 mg), and vinblastine (0.4 mg/kg divided into two daily oral doses repeated every 21 days). Certainly the results of this uncontrolled study are more impressive than those observed with any other combination. Of the group of patients, five had embryonal carcinoma and there were two each with teratocarcinoma, embryonal plus chorio-elements and terato-plus chorio-elements. Six of the patients had lung metastases alone, three had lung metastases with positive lymph nodes, and two had an abdominal mass in a previously radiated field.

While it is hard to believe that the above results can be explained by a patient selection bias, this issue is approached in general by Moertel et al. (Mayo Clinic, Rochester, Minnesota) writing on the effect of patient selection on the results of Phase II chemotherapy trials in gastrointestinal cancer. The authors note that a poor clinical performance status strikingly reduces the likelihood of responding to a chemotherapy trial in GI cancer. They believe that given the meager results with 5-fluorouracil in this disease, it is a patient disservice to withhold newer agents until clear 5-FU failure has been established. They feel that giving 5-FU with a small probability of success results in a weaker clinical condition and a demonstrably poorer response to new agent chemotherapy for GI cancer.