The May/June 1975 issue of Cancer Chemotherapy Reports is heavily slanted to the preclinical area. A major contribution is a series of papers presented at an American Chemical Society Symposium held in Houston, Texas on December 10, 1974, entitled "On the Role of Metal Complexes and Metal Salts in Cancer Chemotherapy." While it is true that most attention has been focused on the cis-platinum complexes, Rosenberg (Michigan State University, East Lansing, Michigan) pointed out in the first paper that there is no reason to believe that platinum complexes are unique in their antitumor activity. This is borne out by other papers by Bear et al. (University of Houston, Houston, Texas) and Adamson and his coworkers (National Cancer Institute, Bethesda, Maryland) which show that rhodium, gallium, aluminum, indium and thallium derivatives also exert antitumor effects in vivo. Lee et al. (University of Houston, Houston, Texas) demonstrated that rhodium (II) acetate was a potent inhibitor in vitro of ara-C deamination by cytidine deaminase. Whether or not this compound would result in modification of the in vivo activity of ara-C remains to be seen, but interest in attempts to modify ara-C metabolism by tetrahydrouridine or use of the depot form cycloxytidine is reflected in other papers in this issue by Neil et al. (Upjohn Company, Kalamazoo, Michigan) and by Liss and Neil (Arthur D. Little, Inc., Cambridge, Massachusetts). The platinum symposium also included papers by Gottlieb and Drewinko (M. D. Anderson Hospital and Tumor Institute, Houston, Texas) and Hill et al. (Wadley Institutes of Molecular Medicine, Dallas, Texas), describing the clinical effects of platinum derivatives. Although substantial toxicity was observed, particularly renal damage, there were also some gratifying tumor responses, e.g., in testicular carcinoma. Combination chemotherapy and examination of other complexes could well result in better therapy and reduced toxicity. Quite fortuitously, a report in this issue by Stadnicki et al. (Mason Research Institute, Worcester, Massachusetts) describes the ototoxicity of cis-dichlorodiammineplatinum (II) in rhesus monkeys, paralleling the findings in the clinic. Normal hearing was restored in the monkeys after 120 and 200 days.

A paper by Jayaram et al. (National Cancer Institute, Bethesda, Maryland) deals with additional biochemical properties of a new antitumor antibiotic from Streptomyces sviceus which appears to act as a potent antagonist of L-glutamine. Inhibition of L1210 cell growth in culture was also
antagonized by the amino acid. A study by Palyi (Christie Hospital and Holt Radium Institute, Manchester, England) describes the survival and phase sensitivity of HeLa cells treated with dianhydrogalactitol and concludes that as with other alkylating agents there is a lack of phase specificity for the drug.

At a time when massive doses of methotrexate are being used therapeutically in conjunction with citrovorum factor (leucovorin) rescue, a brief report by Bruckner and Bertino (Mt. Sinai School of Medicine, New York, New York) makes the useful observation that leucovorin used as a mouthwash, although absorbed systemically, would not reach blood levels high enough to counteract systemic methotrexate. The authors suggest therefore that leucovorin mouthwash should be examined for alleviation of methotrexate-induced mucositis. A report by Finkelstein et al. (Harbor General Hospital, Torrance, California) concludes that murine neuroblastoma does not respond to a treatment schedule using 6-hydroxydopamine, bretylium tosylate, papaverine and butyric acid, and suggests that these agents would probably be ineffective in the treatment of widespread metastatic neuroblastoma in children.

July/August
The July/August 1975 issue contains two items of particular interest to those concerned with the design of drugs and their pharmacokinetics. A guest commentary by Cain (Cancer Chemotherapy Laboratory, New Zealand) discusses the role of structure-activity studies in the design of antitumor agents using log P (the logarithm of the partition coefficients of drugs in the immiscible solvents, water and n-octanol) as his approach. As Cain so aptly states, ‘‘The essential core question is, of course, ‘‘what is the relationship between the optimum log P values of the tumors used in screening and those confronted in the clinic?’’ The need for good pharmacokinetic data on antitumor agents becomes abundantly clear from Chairman Loo’s introductory comments to a series of papers presented at a symposium conducted on the Pharmacokinetics of Antitumor Agents held in New Orleans on November 10, 1974, under the sponsorship of the American Pharmaceutical Association Academy of Pharmaceutical Sciences. The inclusion of papers dealing with the pharmacokinetics of important drugs such as methotrexate, adriamycin, DTIC, ara-C, isophosphamide, as well as theoretical papers by some of the pioneers in antitumor drug pharmaco-
nucleosides, isobutyric, frequently, kinetics, markers, distribution, with, optimal, chemotherapy. (University of Wisconsin), and their coworkers (National Cancer Institute, Bethesda, Maryland). These authors did not observe a significant effect in any of the tumors by either drug used alone and suggest that their value in cancer treatment may be limited to use as adjuvants for chemotherapy or surgery. Zbinden and Brändle (University of Zurich) describe a rat model for the cardiotoxicity of anthracycline drugs based on changes in EKGs and noted a good agreement between their results and clinically observed cardiotoxicity.

The clinical report by Cohen et al. (Roswell Park Memorial Institute, Buffalo, New York) on the phase I trial of isophosphamide, a cyclophosphamide congener, given once every three weeks resulted in toxic manifestations qualitatively similar to those of cyclophosphamide, but careful attention to hydration and bladder irrigation kept the toxicity within manageable limits. A starting dose of 4000-5000 mg./m² was recommended as clinically tolerable for phase II trials on this schedule.

The clinical activity of podophyllotoxin derivatives, VP16-213 and VM26, is described in two papers by Jungi and Senn (Medizinische Klinik C Kantonsspital, St. Gallen, Switzerland) and by Rivera et al. (St. Jude Children’s Research Hospital, Memphis, Tennessee). In the former paper, VP16-213 elicited eight responses among 11 patients with oat cell carcinoma of the lung and four responses among six with ovarian cancer. Treatment was accompanied by considerable leukothrombopenia and alopecia. Rivera et al. using VM26 or VP16-213 did not note activity against diverse solid tumors but did observe nine responses to the drugs among 29 patients with acute leukemia. The toxicity pattern was similar to that reported by Jungi and Senn.