Cancer Chemother Pharmacol (1985) 14 : 177–183

Cancer Chemotherapy and Pharmacology



*Review*

# Anticancer drug pharmacodynamics

**Garth Powis**

Division of Developmental Oncology Research, Department of Oncology, Mayo Clinic, Rochester, Minnesota 55905, USA

***Summary.*** *A considerable amount of information is available on the pharmacokinetics of anticancer drugs, but much less is known of their pharmacodynamics, that is of the relationship between therapeutic or toxic response and drug concentration. Drug dosage regimens which are to achieve defined therapeutic objectives can only be designed when both the pharmacokinetic and the pharmacodynamic characteristics of a drug are known. There are a few reports in the literature of relationships in man between toxic response and pharmacokinetic parameters of anticancer drugs, and an even smaller number of reports of relationships between therapeutic response and pharmacokinetic parameters. It is suggested that the lack of pharmacodynamic information is currently limiting the application of pharmacokinetic information to cancer therapy. Ways of improving knowledge of the pharmacodynamics of anticancer drugs are suggested.*

## Introduction

Considerable effort is being directed toward quantitative clinical pharmacologic studies of anticancer drugs. Quantitative pharmacology has two aspects: first, a pharmacokinetic aspect that relates drug dose, frequency, and route of administration to drug concentration-time relationships in the body; and second, a pharmacodynamic aspect that relates drug concentration at a receptor site to biological response. Since the drug concentration at the receptor site can rarely be measured directly, it is more usual to measure the drug concentration in the plasma and assume that it reflects that at the receptor site. Pharmacokinetic studies have influenced cancer therapy in several ways. Bioavailability studies of PO administered anticancer drugs have shown that some drugs exhibit erratic absorption or variable first-pass hepatic-intestinal metabolism [23, 65], which has led to attempts to develop parenteral formulations for some orally administered drugs [1]. Drug distribution studies can also show whether a drug penetrates relatively inaccessible tissues, such as the brain [9], and, thus, which drugs might be of use for the treatment of tumors located in these areas [61]. The current revival of interest in intracavitary chemotherapy relies heavily on pharmacokinetic predictions of high intracavitary to systemic drug concentration ratios due to slow elimination of hydrophilic drugs from the intracavitary site [21]. Identification of the kidneys or liver as major organs for drug elimination or, more frequently, evidence of delayed plasma elimination of anticancer drugs in patients with renal or hepatic dysfunction has provided a rationale for dose reduction of some drugs in these patients to avoid excessive toxicity [53]. Finally, pharmacokinetic studies can help in the understanding of mechanisms of interactions between anticancer drugs which affect therapeutic activity or toxic side effects [73]. Despite examples such as these, most advances in the way anticancer drugs are given have resulted from clinical empiricism and not from pharmacologic studies. One purpose of this review is to highlight one reason why pharmacokinetic studies have not had a greater impact on the way anticancer drugs are given.

A drug dosage regimen which is to achieve defined therapeutic objectives can only be designed when both the pharmacokinetic and the pharmacodynamic properties of the drug have been characterized [56]. Recent advances in analytical methodology have made sophisticated pharmacokinetic studies of many anticancer drugs possible. On the other hand, we know little of the pharmacodynamic properties of anticancer drugs. This review will discuss problems of studying the pharmacodynamics of anticancer drugs, and it summarizes existing pharmacodynamic knowledge of anticancer drugs with special reference to man. Suggestions are made of ways for improving knowledge of anticancer drug pharmacodynamics.

## 2. Relationship of response to C, C × *t*, or other parameters

Two factors govern the relationship that exists between drug concentration and response: first, whether the drug interacts reversibly or irreversibly with its receptor, and second, whether response is directly or indirectly related to drug concentration. The simplest type of relationship is seen in the case of a drug that interacts reversibly with its receptor, producing a simultaneous biological response that is directly proportional to the concentration of drug at the receptor surface. Some anticancer drugs interact reversibly, while others interact irreversibly with their postulated receptors [8. 70], but in all cases response is indirectly related to drug concentration. The relationship between drug concentration and response is complex and in most cases depends upon cell kinetic phenomena and intracellular processes, of which we have little or no knowledge. Complicating factors are that the drug may first have to be converted by metabolism to an active species, and that it cannot be assumed that the concentration of free drug or active metabolite in the blood is the same as the concentration of free drug at the receptor surface. Solid tumors

*Offprint requests to:* G. Powis

are often poorly vascularized and relatively inaccessible to hydrophilic drugs [74]. Furthermore, toxic responses to anticancer drugs can be delayed and may not become apparent until days, or even weeks, after the drug is given. Response can be difficult to quantify, particularly when a subjective phenomenon such as nausea and vomiting is concerned or when it involves trying to measure the mass of a large and relatively inaccessible tumor.

Theoretical treatments of the pharmacodynamics of irreversibly acting cell-cycle-specific and cell cycle-non-specific cytotoxic drugs have been developed [30, 39, 41, 42]. There is little information, however, even in animals, to permit adequate assessment of the general applicability of such models. In man, because of the problems discussed previously, we are reduced to asking whether response is best related to plasma or serum drug concentration (C), to the integral of concentration × time from time zero to infinity ($C \times t$),to time of exposure above a threshold concentration, to other pharmacokinetic parameters, or to nothing measurable at all. Drugs that interact irreversibly with their receptor, as many anticancer drugs do, often produce an effect that is related to $C \times t$ [31]. $C \times t$ has the advantage that it is less sensitive than C to saturation of pathways of drug elimination at high doses of drug [69], a feature often seen with anticancer drugs [54]. In practical terms, and until more rigorous treatments can be developed, $C \times t$ might prove the best pharmacokinetic parameter for predicting response to an anticancer drug. This is not a new suggestion, and the value of $C \times t$ has been emphasized before [11]. $C \times t$ is the same as the area under the plasma, serum, or blood drug concentration time curve from time zero to infinity (AUC) and is inversely related to total body drug clearance ($C\bar{l}$) by the relationship

$$C \times t = \text{Dose}/C\bar{l}.$$

## 3. Relationship between response and drug exposure

### *3.1. In vitro studies*

Studies with tumor cells in vitro have clearly shown that the cytotoxicity of anticancer drugs depends on both drug concentration and duration of drug exposure [71]. The correlation between cytotoxicity and $C \times t$ is often imperfect and may take the form $C^n \times t$, where n, the concentration exponent, has a value less than 1 [62]. For some drugs, such as hydroxyurea, there is a threshold effect with respect to duration of drug exposure [57], while for other drugs, such as nitrosoureas, that break down to reactive intermediates within the cell, cytotoxicity is only indirectly related to C or $C \times t$ [70].

### *3.2. Pharmacodynamic studies in animals*

Animal studies using drug-sensitive transplantable hematological and solid tumors have consistently shown that therapeutic and toxic responses increase with increasing dose of drug with both single-drug and combination drug treatment [28, 59, 63]. The difficulty of obtaining pharmacokinetic information in individual small animals has precluded studies of the relationship between drug concentration and tumor or toxic response in the same animal [24], although it has been suggested by Schabel et al. [59] that the variability in tumor response and cure rates seen even with inbred mice might be due to individual variation in drug pharmacokinetics. Results of comparative studies in different species have been interpreted as showing a relationship between dose, $C \times t$, and toxicity of anticancer drugs [50]. Freireich et al. [29] showed for several anticancer drugs that equivalent drug doses (on a mg/m$^2$ basis) gave equivalent toxicologic end points in different species. Mellet [49, 50] reported that equivalent (on a mg/m$^2$ basis) doses of cyclophosphamide and methotrexate gave equivalent $C \times t$ values in different species and concluded that, for these drugs at least, equivalent $C \times t$ values give equivalent toxicity in different species [50]. However, inspection of the results of Mellet [49, 50] shows that most of the correlation of dose with $C \times t$ is due to intraspecies correlation and not an interspecies correlation.

### *3.3. Pharmacodynamic studies in man*

*3.3.1. Dose dependency.* Clinical trials have repeatedly shown that the common toxicities of anticancer drugs increase as the dose of drug is escalated. The widely held view that administering an anticancer drug at the maximally tolerated dose is necessary for optimum therapeutic activity against a solid tumor, however, is based on relatively few randomized clinical trials where dose has been a variable [28]. It has been reported that marginally chemosensitive tumors generally fail to display dose dependency, which is not surprising, since increasing the dose of an ineffective drug will only produce an increase in toxicity without altering the therapeutic effect [28].

*3.3.2. Schedule dependency.* There are several examples where marked amelioration in the toxicity of an anticancer drug with no change in therapeutic efficacy has been achieved by giving the drug by slow IV infusion instead of by IV bolus injection. Intermittent bolus administration of doxorubicin every 3 weeks was originally adopted, in part, because of the long biologic half-life of doxorubicin [6]. Evidence then accumulated that weekly administration of doxorubicin produced less cardiotoxicity, although the incidence of other toxicities was unchanged and therapeutic efficacy was maintained [16, 72]. More recently it has been reported that giving doxorubicin, 60 mg/m$^2$ every 3 weeks, by 48-h or 96-h continuous infusion produces less cardiotoxicity and less nausea and vomiting than bolus administration, while mucositis and myelosuppression are unchanged [45]. Because of decreased cardiotoxicity, larger total doses of doxorubicin (600 mg/m$^2$) could be given by infusion than by bolus (465 mg/m$^2$), which may be responsible for an apparent small increase in therapeutic activity of the infusion schedule of doxorubicin administration. Pharmacokinetic studies showed similar plasma $C \times t$ values for bolus administration of doxorubicin and infusion schedules, but with peak plasma concentrations up to 13-fold higher following bolus administration. The results suggest that high peak plasma concentrations of doxorubicin are a contributory factor in increased cardiotoxicity associated with bolus administration. It should be noted that a prediction resulting from theoretical pharmacodynamic models for a cell cycle-non-specific cytotoxic drug, such as doxorubicin, is that the total cytotoxic effect of a given dose of drug is independent of the schedule of administration [41].

Administration of 5-fluorouracil by schedules which avoid high plasma drug concentrations reduces the incidence of myelosuppression. Moertel et al. [51] compared the effect of the same dose of 5-fluorouracil administered over several days by IV bolus injection (15 mg/kg for 5 consecutive days followed

by 7.5 mg/kg every other day for 4 doses) and by slow IV infusion (22.5 mg/kg over 8 h for 5 consecutive days) and found the incidence of leukopenia to be decreased from 83% to 6% with slow infusion, although there was no difference in the objective response rate. Other studies have reported an increase in response rate for 5-fluorouracil administered by infusion [60]. Concomitant pharmacokinetic studies to measure plasma 5-fluorouracil concentrations were not conducted by Moertel et al. [51]. While it is reasonable to assume that peak plasma concentrations of 5-fluorouracil were lower with slow infusion than with bolus administration it cannot be assumed that similar $C \times t$ values were attained by the different administration schedules. Hepatic elimination of 5-fluorouracil exhibits saturation at high concentrations. Using doses and schedules of 5-fluorouracil administration similar to those used by Moertel et al. [51], Cano et al. [14] found that total body 5-fluorouracil plasma clearance was 800 ml/min after rapid injection but 20.7 l/min after infusion. Plasma $C \times t$ values for 5-fluorouracil will, therefore, be proportionately greater following rapid injection than following slow infusion.

Prolonged IV infusion of cisplatin has been reported to produce less toxicity than rapid IV infusion, with no change in antitumor activity [46–48]. Pharmacokinetic studies have shown no change in $C \times t$ of free platinum or in the species of free platinum whether the same dose of cisplatin (100 mg/m$^2$) is administered by rapid infusion or by short- or long-term infusion [52, 68].

In contrast to the anticancer drugs discussed above, the severity of methotrexate's toxicity increases as the infusion time is increased and appears to be determined primarily by the extent by which a time threshold, rather than a concentration threshold, is exceeded [8]. Goldie et al. [32] found that methotrexate infusions giving peak plasma concentrations of $5 \times 10^{-4}$ $M$ resulted in significant myelosuppression only when leucovorin rescue, which reverses the effects of methotrexate, was delayed more than 36 h after the start of methotrexate infusion. Bleyer [8] has estimated the toxicity concentration and time thresholds of methotrexate for bone marrow and gastrointestinal epithelium to be $2 \times 10^{-8} M$ and 42 h, respectively.

*3.3.3. Toxic response and pharmacokinetic paramters.* A summary of anticancer drugs for which toxicity has been linked to one or more pharmacokinetic parameters is given in Table 1. In a preliminary report, Byfield et al. [12] claimed a positive linear correlation between a number of toxic effects of 5-fluorouracil, except CNS toxicity, and serum 5-fluorouracil concentrations in patients receiving 5-fluorouracil by 3- to 5-day infusion. In an earlier study, however, Hillcoat et al. [38] found no difference in the $C \times t$ for plasma 5-fluorouracil in patients who did and did not experience toxic effects while receiving a 5-day infusion of 5-fluorouracil. 5-Fluorouracil has been administered together with thymidine, which blocks the rate-limiting step in the hepatic metabolism of 5-fluorouracil [73]. Au et al. [2] reported that when 5-fluorouracil was administered by continuous infusion together with a bolus dose of thymidine the incidence of leukopenia was greatest in patients with a low plasma 5-fluorouracil clearance.

Campbell et al. [13] have reported a correlation between plasma levels of total platinum and the subsequent development of nephrotoxicity in patients receiving the same dose of cisplatin by 24-h IV infusion. Crom et al. [20] reported that pediatric patients in whom plasma total platinum increased with successive courses of cisplatin therapy were more likely to develop ototoxicity than patients showing no increase in plasma total platinum. Plasma total platinum represents, predominantly, platinum covalently bound to plasma protein, and animal studies have shown that although free platinum species are nephrotoxic, protein-bound platinum is devoid of nephrotoxicity [18]. It is possible, however, that total platinum in plasma reflects the amount of free platinum available during or immediately after infusion, and it might provide an indirect measure of exposure to reactive platinum species, thus explaining the results of Campbell et al. [13]. Egorin et al. [26] have recently reported that following administration of carboplatin, a cisplatin analogue, the reduction in platelet count correlates with $C \times t$ of free platinum in plasma.

Fludarabine is a nucleotide analogue, and Hersh et al. [37] have reported a correlation between $C \times t$ of free fludarabine in plasma and neutropenia and granulocytopenia.

Liver dysfunction can lead to delayed drug elimination when the liver is a major pathway for elimination of the drug. Benjamin et al. [7] first reported that patients with impaired liver function receiving doxorubicin, which is eliminated primarily by the liver, experienced more toxicity, characterized by mucositis and pancytopenia, than patients with normal liver function. Furthermore, elimination of doxorubicin and its metabolites was delayed and plasma concentrations were 4- to

**Table 1.** Correlation between pharmacokinetic parameters and toxicity

| Drug | Parameter | Toxicity | Reference |
|---|---|---|---|
| Doxorubicin | C | Mucositis, pancytopenia | [7] |
| | C | Granulocytopenia | [19] |
| | C | Cardiotoxicity, nausea | [45] |
| | $C \times t$ | Mucositis | [10] |
| Bruceantin | $\bar{Cl}$ | Hypotension | [27] |
| Carboplatin | $C \times t$ | Thrombocytopenia | [26] |
| Carminomycin | $C \times t$ | GI, cardiotoxicity | [44] |
| | C (total) | Ototoxicity | [20] |
| Fludarabine | $C \times t$ | Neutropenia, granulocytopenia | [37] |
| Cisplatin | C (total) | Nephrotoxicity | [13] |
| 5-Fluorouracil | C | Stomatitis, GI, myelosuppression | [12] |
| 5-Fluorouracil/thymidine | $\bar{Cl}$ | Leukopenia | [2] |
| m-AMSA | $\bar{Cl}$ | Thrombocytopenia | [34] |
| Methotrexate | C, $t$ (threshold) | Myelosuppression | [32] |
| Vincristine | $C \times t$ | Neurotoxicity | [22] |

C, concentration; $t$, time, $\bar{Cl}$ total body clearance

5-fold higher in patients with liver dysfunction than in patients with normal liver function. Based on these observations, patients with varying degrees of liver dysfunction were subsequently treated with reduced doses of doxorubicin and achieved similar plasma $C \times t$ values, and similar toxic and therapeutic responses, to patients with normal liver function [3, 7]. Brenner et al. [10] have recently reported a study of doxorubicin pharmacodynamics in patients with acute nonlymphocytic leukemia (ANLL), where decreasing the dose of doxorubicin given to patients with abnormal liver function resulted in lower plasma $C \times t$ values for doxorubicin and metabolites, less toxicity (mucositis), but no change in therapeutic response rate compared to patients with normal liver function. Furthermore, mucositis was not increased in patients with mild hepatic dysfunction who received full doses of doxorubicin. The authors concluded that the dose-response curve for doxorubicin in ANLL, if one exists, is very shallow. Lankelma et al. [44] have reported a trend for $C \times t$ of plasma carminomycin, a doxorubicin analogue, and its metabolite to be higher in patients experiencing the greatest carminomycin-induced gastrointestinal and cardiactoxicity. The liver function status of the patients was not reported in this study.

Vincristine is another drug eliminated primarily by the liver. The major limiting factor in the use of vincristine is neurotoxicity. Desai et al. [22] have reported a correlation between $C \times t$ of plasma vincristine following initial therapy and the degree of neurotoxicity. $C \times t$ for plasma vincristine was related both to dose of vincristine and to liver dysfunction measured by an elevated serum alkaline phosphatase. Other drugs where liver dysfunction has been shown to be a cause of decreased total body drug clearance and an increase in toxicity in the same patient are m-AMSA [34] and bruceantin [27].

Toxicity associated with prolonged exposure to methotrexate has been discussed previously. Renal excretion is a major route for elimination of methotrexate, and delayed elimination of methotrexate owing to poor renal function or associated with an increased third space of distribution, as with ascites or pleural effusion, is associated with increased myelosuppression and gastrointestinal toxicity [9, 64]. There are a number of other anticancer drugs whose elimination is delayed and toxicity increased in patients with renal dysfunction [53]. These drugs are not discussed here, because pharmacokinetic parameters have not been correlated with toxicity in the same patient.

*3.3.4. Therapeutic response and pharmacokinetic parameters.* There are a few reports, summarized in Table 2, of a correlation between therapeutic response and pharmacokinetic parameters of anticancer drugs in individual patients. Baguley and Falkenhaug [4, 5] reported that plasma concentrations of cytosine arabinoside were significantly higher in patients with acute myeloblastic leukemia (AML) who responded to treatment than in patients who did not respond. The results of these studies showed considerable variability in plasma cytosine arabinoside concentrations even in the same patient receiving successive courses of treatment. Van Prooijen et al. [66, 67] subsequently reported delayed plasma elimination of cytosine arabinoside in patients with AML who responded well to treatment, who had a terminal plasma half-life greater than 12.7 min, compared with patients who responded poorly to treatment, who had a terminal plasma half-life between 6.6 and 10.7 min. These reports of a correlation between response and pharmacokinetic parameters of cytosine arabinoside have not been confirmed by more recent studies. Harris et al. [36] could find no correlation in patients with AML between remission or the fall in peripheral blast cell count and cytosine arabinoside exposure expressed as $C \times t$ or as total body clearance. Early et al. [25] also reported no correlation between plasma cytosine arabinoside concentration and therapeutic response or toxicity in patients with AML. It is, perhaps, not surprising that response to cytosine arabinoside does not correlate with plasma concentrations of drug. Cytosine arabinoside is rapidly inactivated by cytidine deaminase, but inhibition of deamination does not increase the therapeutic index of cytosine arabinoside [43], and measurement of deaminase activity is of no help in selection of patients who will respond [35]. Cytosine arabinoside is not the active agent, and only a small proportion of drug is converted in tissues to the active metabolite cytosine arabinoside triphosphate. Studies performed in marrow myeloblasts from patients with AML suggest that a poor response to therapy with cytosine arabinoside might be related to low rates of synthesis of cytosine arabinoside triphosphate or to low levels of deoxycytidine kinase, which is thought to catalyze the rate-limiting step in cytosine arabinoside activation [17, 35].

**Table 2.** Correlation between pharmacokinetic parameters and therapeutic response

| | Parameter | Disease site | Responders / Nonresponders | Reference |
|---|---|---|---|---|
| Cisplatin | $C \times t$ (free) | Tongue/ovary | 3 (total) | [68] |
| Cytosine Arabinoside | C | AML | 4/6 | [4] |
| | $t_{1/2}$ | AML | 1/7 | [5] |
| | $t_{1/2}$ | AML | 9/5 | [67] |
| (No correlation) | $\bar{Cl}$, $C \times t$ | AML | 5/9 | [36] |
| (No correlation) | C | AML | 9/7 | [25] |
| Doxorubicin | C | ANLL | 37/45 | [55] |
| 5-Fluorouracil | C, $C \times t$ | | 6/12 | [33] |
| | $C \times t$ | Gastrointestinal | 8/19 | [38] |
| | $\bar{Cl}$ | Gastrointestinal | 6/6 | [15] |
| Vinblastine | $\bar{Cl}$, $C \times t$, $t_{1/2}$ | Breast | 4/8 | [48] |

C, concentration; $t$, time; $t_{1/2}$, half-life; $\bar{Cl}$, total-body clearance. Responders, number of patients responding to treatment; nonresponders, number of patients with no response to treatment

Iacoboni et al. [40] have reported that the peripheral blast cells of patients with relapsed acute leukemia who respond to high-dose cytosine arabinoside therapy have levels of cytosine arabinoside triphosphate greater than 75 $\mu M$. The authors used appropriately shortened dose intervals for cytosine arabinoside in individual patients to achieve the desired levels of cytosine arabinoside triphosphate and reported an increased reponse rate.

There have been reports of a correlation between plasma concentrations of 5-fluorouracil and therapeutic response. Hillcoat et al. [38] reported that patients with metastatic gastrointestinal cancer who received 5-fluorouracil as a continuous 5-day IV infusion and who showed partial response or stabilization of disease had higher plasma 5-fluorouracil $C \times t$ values than patients who did not respond. There have been other preliminary reports of a correlation between response to 5-fluorouracil and plasma drug concentrations, but with insufficient detail in the reports to allow adequate evaluation. Gudauskas and Goldie [33] reported a correlation between the presence or absence of therapeutic response and plasma 5-fluorouracil concentration and $C \times t$ in patients receiving a 4- to 5-day continuous IV infusion of 5-fluorouracil. Cano et al. [15] reported a group of patients with gastrointestinal cancer, where patients with response or stabilization of disease with 5-fluorouracil had a total-body 5-fluorouracil clearance less than 720 ml/min, while patients with progressive disease had total-body 5-fluorouracil clearance greater than 720 ml/min. It is likely that low therapeutic response rates associated with 5-fluorouracil compared with some other anticancer drugs will make it difficult to establish an unequivocal relationship between therapeutic response and plasma 5-fluorouracil concentrations.

Preisler et al. [55] studied single time point (3 h) doxorubicin and doxorubicinol plasma concentrations in patients with ANLL receiving doxorubicin by rapid infusion daily for 30 days. A modest but significant correlation was found between duration of remission and the plasma doxorubicin and/or doxorubicinol concentration on day 1, although not on days 2 or 3. In a study discussed previously, Brenner et al. [10] reported a small but nonsignificant decrease in duration of response and survival in patients with ANLL and liver dysfunction receiving reduced doses of doxorubicin, who had a lower plasma $C \times t$ for doxorubicin and metabolites than patients with normal liver function.

Lu et al. [48] reported a favorable clinical response associated with delayed elimination of vinblastine in patients with breast cancer receiving a 5-day continuous IV infusion of the drug.

## 4. Conclusions

Our knowledge of relationships between drug concentration and response to anticancer drugs in man is rudimentary. Pharmacodynamic information is, however, essential if pharmacokinetic principles are to be used to improve the way anticancer drugs are given. We might ask whether anything can be done to improve our understanding of the pharmacodynamics of anticancer drugs, given the limitations of current knowledge of the way most anticancer drugs produce their biological effect and the problems, discussed previously, of measuring drug concentrations at the receptor surface. The answer is yes. Several lessons can be learned from studies conducted so far. First, wherever possible, pharmacokinetic studies should accompany clinical studies where the schedule of drug administration is changed, so that altered biological response can be related to changes in drug exposure. Second, when choosing drugs to study it is clearly easier to relate drug pharmacokinetics to therapeutic response with an active drug than with a drug with little activity. Third, pharmacokinetic studies should be conducted in a wide range of patients, including patients with hepatic or renal dysfunction, in the early stages of clinical development of a drug when it is being used as a single agent. Fourth, every effort should be made to present for each patient studied pharmacokinetic data, the type and degree of toxicity, and the therapeutic response. Fifth, sufficient numbers of patients should be studied to allow statistically meaningful correlations to be made between pharmacokinetic parameters and toxicity and therapeutic response. This will almost certainly mean that larger numbers of patients will have to be studied to correlate therapeutic response to drug pharmacokinetics than to correlate most toxic responses. Sixth, attempts should be made to measure drug concentrations within the tumor and other tissues and, ideally, the drug concentraton at the subcellular target site. Finally, it will be important to conduct parallel studies in animals, where tumor response is more readily measured than in man, to establish correlations between drug pharmacokinetics and tumor response in individual animals. Using these approaches it is to be hoped that our understanding of anticancer drug pharmacodynamics will advance to the point where pharmacokinetic information can be more widely used to improve cancer therapy, to enhance therapeutic effect, and to decrease toxic side effects of anticancer drugs.

*Acknowledgement.* The excellent secretarial assistance of Ms Wanda Rhodes is gratefully acknowledged.

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Received September 7, 1984/Accepted October 3, 1984