1. INTRODUCTION

Large amounts of data on tumor cell survival as a function of exposure to anticancer drugs, drug pharmacokinetics, drug distribution in the body, and other aspects of drug delivery and effectiveness are continually being generated. Cancer therapies are becoming increasingly complex, and it is now possible to choose the time schedule of drug delivery, the site of delivery, the size, lipophilicity, release kinetics and other properties of a carrier, and numerous other options. However, it is clearly impossible to perform sufficient animal experiments or clinical trials to determine the optimal choices of all these variables. Even for drugs that have been used for decades, doses and schedules are often based on past experience and medical tradition rather than on rational analysis. These circumstances suggest an increasing need for theoretical models of anticancer drug delivery. Such models can provide a framework for synthesizing and interpreting available experimental data, and a rational basis for optimizing therapies using existing drugs and for guiding development of new drugs.

A synthesis is needed of two main bodies of anticancer drug research: studies on cellular responses to drugs, and studies on how the method of drug administration affects an animal or patient. Improved understanding is needed of the relation between the mode and schedule of therapy and the resulting drug exposure of cancer cells and normal cells that are responsible for limiting toxicities. This requires consideration of
the steps involved in drug transport from the infusion site to the tumor (1-3). Here, theoretical modeling can play an important role, by predicting cellular exposure and toxicity as a function of treatment mode and schedule, taking into account whole-body pharmacokinetics and transport processes leading to spatial and temporal variations of drug concentrations within the tumor and other tissues.

The focus of this review is on the use of theoretical models to investigate the relationship between delivery of anticancer drugs and their cellular effects, with the goal of optimizing anticancer therapies. First, theoretical models for the dependence of tumor cell kill on cellular drug exposure are considered. The importance of host tissue toxicity is then discussed. Next, studies aimed at optimizing intravenous (iv) delivery are examined, along with studies on alternative delivery methods. Finally, potential directions for future research are considered.

2. ANTITUMOR EFFECTS OF CELLULAR DRUG EXPOSURE

Several theories have been developed to describe the relation between cellular exposure to anticancer drugs and effect, measured as tumor cell kill or surviving fraction of clonogenic cells. In this context, “exposure” refers to the time course of extracellular concentration. Because response to a drug generally increases with increased drug levels and with increased exposure time, the area under the (extracellular) concentration-time curve, generally called AUC, is often used as a predictor of effectiveness. In most in vitro experiments, the extracellular concentration is held constant, so that AUC is $C \times T$, the product of extracellular concentration and exposure time. Data sets with only one exposure time (and several different concentrations) or only one concentration (and varying exposure time) cannot be used to test whether AUC by itself properly predicts drug effect. Data on cell kill for different combinations $C_1 T_1 = C_2 T_2$ where $C_1 \neq C_2$ are needed. Walker et al. (4) and Erlichman et al. (5) obtained such data for two different human bladder cancer cell lines and concluded that AUC alone predicted cell kill. Walker et al. (4) reported this observation for doxorubicin, epodyl, mitomycin C, and thiotepa; Erlichman et al. (5) found it to hold for melphalan, cisplatin, doxorubicin, mitomycin C, and 5-fluorouracil, but not for vincristine. Ozawa et al. (6) concluded that AUC predicts cell kill for Chinese hamster cells exposed to mitomycin C, from their data showing that log(IC$_{90}$) (where IC$_{90}$ is the concentration required for 90% growth inhibition) plotted vs log(T) is linear with slope $-1$. Kurihara et al. (7) exposed gastric cancer cell lines to cisplatin for different times, and also concluded that AUC was a predictor of effect.

A cell kill that depends only on AUC, independent of the time course of concentration, is to be expected if the proportional rate of cell kill is linearly related to the concentration. In particular, if cell kill is rapid enough to be considered instantaneous, then cell kill is dependent only on AUC, if and only if the number of cells $n(t)$ satisfies

$$
\frac{1}{n} \frac{dn}{dt} = -kc
$$

[Eq. 1]

where $c(t)$ is the drug concentration and $k$ is a constant. Linear models for cell kill are clearly limited in their applicability. Most pharmacologic responses are nonlinear in concentration, showing saturation at high levels. Furthermore, cooperative behavior is often seen at low-concentration levels, giving a sigmoidal dependence of response on concentration. In such cases, AUC alone cannot predict cell kill. For example, the effects of doubling the concentration and halving the exposure time (while holding AUC constant) do