The design of cancer chemotherapeutic agents would already have evolved from empiricism to rationalism if a unique structural feature exists that specifically confers anticancer activity on a chemical substance. In reality, the structures of anticancer drugs vary widely; this structural diversity dictates a similar diversity in the pharmacokinetics and metabolism of these drugs. Generally however, the pharmacological disposition and metabolism of a particular class of anticancer agents, the antimetabolites, closely mimic those of their natural counterparts, and a reasonable extrapolation can frequently be made.

Except for the nitrosoureas, the majority of anticancer drugs are poorly and varyingly absorbed. As an example, the important antimetabolite 5-fluorouracil (5-FU) is incompletely absorbed in man (1), although it is apparently actively transported in vivo across the intestinal epithelium (2). In view of the steep dose-response of anticancer drugs, their erratic and inconsistent gastrointestinal absorption makes it difficult to predict clinical response and toxicity. In addition, "first-pass" hepatic degradation of the orally administered drug materially reduces the effective drug level. These disadvantages seriously offset the convenience of oral administration of an antitumor agent.

In common with any other drug, an anticancer agent that is highly lipid-soluble, not appreciably ionized at body pH, and not extensively bound to proteins, tends to penetrate plasma membranes with ease. But too high a lipid solubility may prove to be a disadvantage since the drug will remain localized in the membrane lipoprotein and fail to diffuse intracellularly. Besides passive diffusion, many anticancer agents are transported by a variety of
carrier-mediated mechanisms such as active transport and facilitated diffusion. One must be aware, however, that concentrative uptake is not always an active process. Frequently an antitumor drug is biotransformed inside the cell to a metabolite that effluxes only with difficulty resulting in intracellular trapping; the concentrative uptake of ribosyl-6-methylthiopurine by human leucocytes exemplifies this (3).

An anticancer drug with a close structural relationship to a natural metabolite often shares with it a common transport mechanism; for instance, methotrexate (MTX) and folate (4), mechlorethamine (HNZ, nitrogen mustard) and choline (5), 5-fluorouracil and uracil (1).

One of the distressing clinical problems confronting the chemotherapist in the treatment of cancer is the failure of most anticancer agents to reach malignant cells sequestered in the so-called anatomical sanctuaries such as the central nervous system (CNS); 6-mercaptopurine (6-MP) (3), MTX (6), dacarbazine (DIC) (7), and thiopurine nucleosides (8) are typical examples of antitumor agents that do not noticeably penetrate the blood-brain barrier. In contrast, 5-FU (9) and ftorafur, the 1-(2-tetrahydrofurfuryl)-derivative of 5-FU (10), can achieve a significant level in the CSF after intravenous administration. As expected, large protein molecules, like L-asparaginase with a molecular weight of about 140,000 daltons, are denied entry to the CNS (11). By virtue of their lipid-solubility, the nitrosoureas cross the blood-brain barrier with ease (12, 13). But besides lipid-solubility, other factors also influence the entry of an antitumor drug to the CNS. Though extremely soluble in lipids, the di-n-amyl ester of MTX is not detectable in the CNS of dogs injected with this drug, most likely because of its quick metabolism to an ionizable product that fails to cross the blood-brain barrier (14).

When an agent is directly introduced into the systemic circulation, the plasma is the only body compartment immediately permeable to the drug, and it is also the only tissue in which in vivo drug concentration and distribution can be readily assessed with some certainty. Nevertheless, plasma drug levels are rarely representative of those in other body compartments. Yet the sampling of tissues other than the plasma normally involves considerable risk except post mortem; consequently, information on drug distribution therein must be inferred indirectly. To this end elegant mathematical models have been constructed, which have shown promise to predict tissue drug levels at different intervals (15, 16).

Once in the systemic circulation, the drug will be removed by a number of processes, including excretion, biotransformation, and storage in body depots. Traditionally the efflux rate of the drug from the plasma is expressed in terms of its "half-time". Such an