edited by
Stanley T. Crooke and
Archie W. Prestayko

# Cancer and Chemotherapy

## VOLUME III

## ANTINEOPLASTIC AGENTS

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# CANCER AND CHEMOTHERAPY

*Volume III*

## Antineoplastic Agents

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# GENERAL PREFACE

With the rapid development of new chemotherapeutic approaches and new agents used in the treatment of patients with cancer, a basic textbook describing in some detail the drugs currently employed, current therapeutic approaches, and agents in development is essential. However, to understand fully cancer chemotherapeutic agents and their use, one must understand various aspects of anticancer drug development, the molecular and cellular biology of malignant disease, and the clinical characteristics of the most common neoplasms. Only with this information can a detailed discussion of anticancer drugs be presented.

It was with these thoughts in mind that "Cancer and Chemotherapy" was developed; the goal: to provide in a single text the information necessary for a detailed understanding of the major antineoplastic agents. Thus, Volume I is designed to provide the fundamental information concerning the molecular and cellular biology of cancer, carcinogenesis, and the basics of anticancer drug development. Volume II provides clinical information relative to the most common human malignancies and discusses the use of chemotherapeutics in the treatment of those diseases. In Volume III the antineoplastic agents are discussed. It contains reviews of all the major anticancer drugs and a review of agents in development. Furthermore, in two sections—the molecular pharmacology of selected antitumor drugs, and the clinical pharmacology of selected antitumor drugs—significantly more detailed discussions of certain drugs are provided. These drugs were selected because they have interesting characteristics and adequate data are available to allow a more detailed discussion. These two sections should be of particular value to individuals who have an interest in certain aspects of particular drugs.

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# PREFACE TO VOLUME III

In this volume, a discussion is presented in Part I of clinically useful anticancer drugs with respect to their mechanism of action, pharmacology, and pharmacokinetics, clinical utility, and associated toxicities. The various drug classes include alkylating agents (cyclophosphamide, nitrosoureas, mitomycin C, and others), plant alkaloids (vinca alkaloids, podophyllotoxin derivatives, maytansine), antibiotics (bleomycin, anthracyclines), platinum-containing complexes, antimetabolites and hormones. A brief description of investigational agents is provided. This section is concluded by a discussion of a new technique that is used to grow tumor cells in culture and to test the sensitivity of these cells to various anticancer drugs.

Part II presents a detailed discussion of the molecular pharmacology of several major drug classes.

Part III presents an in-depth discussion of the clinical pharmacology of several antitumor drugs. This section is limited to the drugs for which suitable assays have been developed and sufficient clinical data have been obtained.

Stanley T. Crooke
Archie W. Prestayko

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# Part I
# General Reviews

# 1
# NUCLEOSIDE ANALOGUES

Bruce A. Chabner



## I. INTRODUCTION

The nucleoside analogues form a chemically large group and represent attempts to prepare new antineoplastics by rational synthesis. They can be divided into several structural groups, and a number of the agents are important drugs.

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## II. CYTOSINE ARABINOSIDE

Cytosine arabinoside (1-β-D-arabinofuranosylcytosine) (Fig. 1), also known as ara-C, was synthesized in 1959 and has since been recognized as the most active antimetabolite for remission induction in adult nonlymphocytic leukemia (Ellison, 1968). It is currently used with anthracyclines in the standard induction regimens for this disease, achieving 60–70% complete remissions in unselected cases (Kremer, 1975). It has also found limited usefulness in the treatment of meningeal leukemia or lymphoma for patients resistant to methotrexate or in patients experiencing methotrexate-related neurotoxicity (Band *et al.*, 1973).

### A. Mode of Action

Cytosine arabinoside functions as an analogue of the naturally occurring nucleoside 2′-deoxycytidine (Fig. 1). The primary cytotoxic effect of cytosine arabinoside is believed to be inhibition of DNA polymerase by cytosine arabinoside triphosphate (ara-CTP), although the drug is also known to be incorporated into both RNA and DNA to a limited extent (Chu, 1971; Momparler, 1972; Rashbaum and Cozzarelli, 1976). Both semiconservative, or replicative, DNA synthesis, and unscheduled, or "repair," synthesis are inhibited, although the former appears to be more sensitive to inhibition; although maximum sensitivity of cells occurs during the S- or DNA-synthetic phase of the cell cycle, treatment of cells in other phases, such as $G_2$ or $G_1$, leads to chromatid deletions (Brewen and Christie, 1967; Hiss and Preston, 1978). Cells exposed to ul-

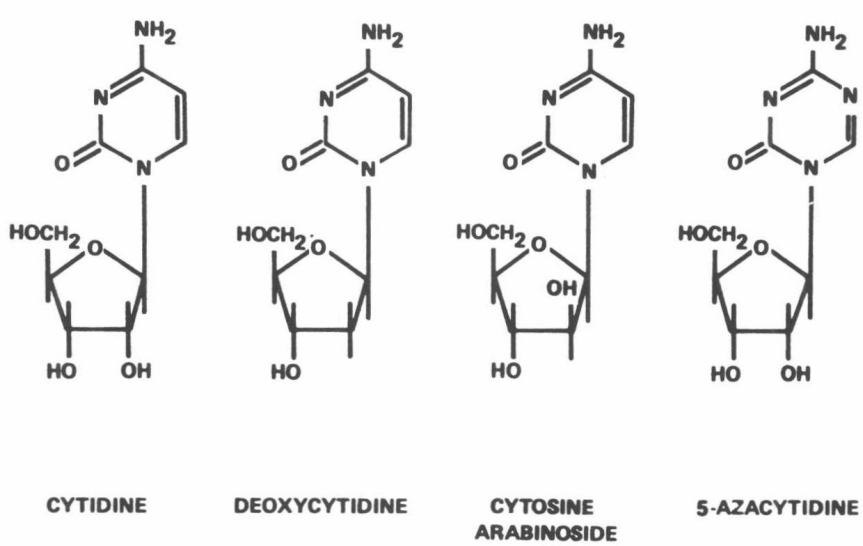


**Fig. 1.** Structure of cytidine, deoxycytidine, and antitumor analogues.

traviolet irradiation are unable to repair single-strand breaks in DNA in the presence of ara-C (Hiss and Preston, 1978).

In order to achieve activation to ara-CTP, the nucleoside must enter the target cell, a process believed to occur by facilitated diffusion. Thereafter, a series of phosphorylation steps occurs (see Fig. 2), utilizing the same enzymes required by the physiologic nucleoside deoxycytidine in its activation to a triphosphate. The slight alteration in structure of the sugar moeity of ara-C renders it a somewhat less favorable substrate for deoxycytidine kinase, but a more active substrate for deoxycytidine monophosphate kinase (the second step in the pathway) (Hande and Chabner, 1978). The drug is also susceptible to degradation by cytidine deaminase, an enzyme found in liver, gastrointestinal tract, plasma, and some tumor cells and by deoxycytidine monophosphate deaminase, which is also found in leukemic cells as well as spleen and liver. The products of deamination of ara-C and cytosine arabinoside monophosphate (ara-CMP) are both inactive in terms of cytotoxicity. The nucleoside deaminase, found in high concentrations in human liver (Stoller *et al.*, 1978), is primarily responsible for ara-C elimination, but the possible role of these enzymes in resistance of tumors to ara-C requires further evaluation. Preliminary studies (Stoller *et al.*, 1975) indicate that the monophosphate deaminase is present in higher concentrations than the nucleoside deaminase in malignant cells.

Multiple mechanisms of drug resistance have been described in animal tumor systems, including deletion of the activating enzyme, deoxycytidine kinase (Draharosky and Kreis, 1970), and increased *de novo* synthesis of dCTP

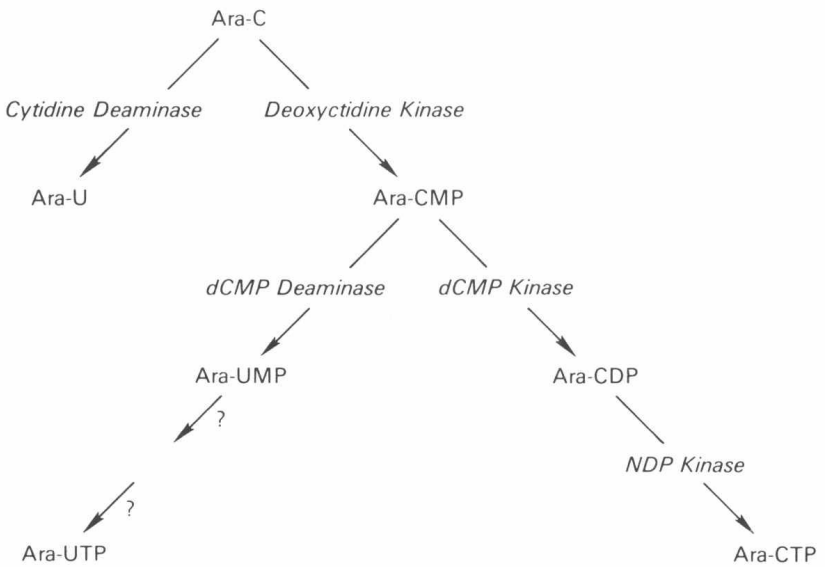


**Fig. 2.** Intracellular metabolism of cytosine arabinoside. Enzymes are indicated by italics. Tetrahydrouridine blocks cytidine deaminase, the first catabolic enzyme in the pathway.