ANTINEOPLASTIC AGENTS

Edited by

William A. Remers

A volume in the Wiley series,
CHEMISTRY AND PHARMACOLOGY OF DRUGS
Daniel Lednicer, Editor-in-Chief

ANTINEOPLASTIC AGENTS

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ANTINEOPLASTIC AGENTS

CHEMISTRY AND PHARMACOLOGY OF DRUGS

A Series of Monographs

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Series Preface

The process of drug development has undergone major changes in the last two decades. To appreciate the magnitude of the change, one needs to think back to the mid-1950s. This was the boom period of pharmaceutical development; better than half the structural classes available to today's clinician had their inception in that era. Yet, in spite of all the demonstrable successes, this was not a period of truly insightful research. Rather, regulations were sufficiently liberal so that novel chemical entities could be—and were—taken to the clinic with only a demonstration of safety and some preliminary animal pharmacology. It is perhaps as a result of this that many of our pharmaceutical mainstays owe their existence to serendipitous clinical findings.

It should, of course, be added that the crude nature of the available pharmacology was a reflection on the state of the art rather than on a desire to skimp on research. A good many of the current concepts in pharmacology postdate the boom era in drug development.

The same applies to medicinal chemistry. With a few notable exceptions, much of the synthesis was aimed at achieving a patentable modification on someone else's drug or consisted in following "interesting chemistry" in the hope of coming up with biological activity. The dialogue between the medicinal chemist and the pharmacologist was in its infancy.

The drug development process in 1982 is an entirely different discipline; though the time and effort involved in taking a drug from the bench to registration has increased enormously, it has, in spite of this, become more intellectually satisfying. The increased knowledge base permits more informed decisions.

The increased stake involved in taking a drug to the clinic means that upper management in drug companies wants greater assurance of success be-

fore taking that very expensive step. Consequently, compounds are studied pharmacologically in far greater detail than ever. The gap between animal pharmacology and human therapy is being steadily narrowed by the development of ever more sophisticated tests which may more accurately forecast human responses. Much of this has been made possible by enormous strides in pharmacology. Understanding of drug action is approaching the molecular level.

Medicinal chemistry too has acquired a firmer theoretical underpinning. The general desideratum is rational, or directed, or deliberate, drug development. (*Rational* strongly implies that those who do not follow that design are irrational. There is too large an element of luck, serendipity, and informed intuition involved in drug discovery to use the term irrational for those who choose a more intuitive approach.) This approach has in fact achieved its first success: Cimetidine was developed by studying the interaction of histamine and its congeners with its receptors. Captopril came from a research program motivated by a consideration of the role of the renin angiotensin system in the control of blood pressure.

A hallmark of many laboratories involved in drug development is the existence of the project team. All individuals assigned to research on drugs in a given therapeutic area are expected to interact with a greater or lesser degree of formality and to make their own day-to-day research decisions in close consultation. While the makeup of such teams varies considerably, the medicinal chemist and the pharmacologist are almost obligatory members. It becomes incumbent on each to be able to communicate with the other. The pharmacologist will thus profitably be acquainted with the names and, if possible, structures of compounds relevant to the therapeutic area, be these drugs or endogenous agonists and antagonists. While not expected to actually design analogue series, the pharmacologist may find it appropriate to be able to recognize pharmacophoric groups. The chemist, on the other hand, will certainly want at least nodding acquaintance with the pharmacological basis for drug therapy in an assigned area. An understanding of biological screens, tests, and their limitations will help the chemist better understand the biological significance of test results on compounds being studied.

There are today very few convenient sources to which a scientist can turn for such information. As a rule the pharmacology on any therapeutic area will be scattered in original articles and reviews in the biological literature. An individual seeking the medicinal chemistry background will have to choose between consulting superficial reviews, perusing some sixteen or more

volumes of highly condensed periodic reports, or going back to the original literature.

Chemistry and Pharmacology of Drugs is a series of books intended to allow scientists involved in drug development to become familiar with specific therapeutic areas by consulting a single volume devoted specifically to that area.

Each of the volumes of the series envisaged treats a fairly discrete disease entity, or sometimes a therapeutic class. Each of the books treats separately the pharmacology, screening, and development methods and medicinal chemistry relevant to the topic. In each book, the first section deals in some detail with both the normal and diseased physiology of the appropriate organ system; it is in this section that the pharmacology and, if pertinent, biochemistry are discussed. The next section deals with the various primary screens that have been used to discover active compounds. More elaborate tests designed to elucidate mechanism of action and the like are discussed as well. The medicinal chemistry section deals with the chemistry used to prepare active compounds; where available, the SAR of active series; and the rationale that led a particular direction to be chosen. Since such a volume is today beyond the scope of any single author, each book will be written by three or, at the most, four authors.

DANIEL LEDNICER
Series Editor

Preface

Progress in the discovery of new cancer chemotherapeutic agents has been unspectacular, considering the amount of money and talent expended in this field. When viewed, however, from the perspective that cancer is an extraordinarily complicated and resilient group of diseases which offers few targets for chemotherapy, the progress is rather admirable. The fundamental difficulty in developing useful antitumor agents is the lack of selectivity between tumor cells and normal cells. Most of the differences on which selective toxicity must be based are quantitative rather than qualitative, a more difficult situation than, for example, the selective killing of bacterial cells whose qualitative differences from mammalian cells in terms of cell walls and ribosomes present highly selective targets for cytotoxic drugs.

Despite the lack of unique targets in cancer cells, it is often possible to reduce their numbers drastically without destroying the contiguous normal cells. A thousandfold reduction in cancer cells can be produced by a number of drugs. Unfortunately, to effect a cure it may be necessary to kill all the cancer cells. Because the drugs kill a constant fraction of the cancer cells, increasing amounts are required to bring the cell count down to low numbers, and there is a high probability that serious toxicity to normal cells will occur in the meantime. In theory, the body's immune system should be able to dispose of the remaining small amounts of aberrant cells. But by their very nature the cancer cells have managed to elude or overcome the immune system. The final eradication of cancer cells is unlikely unless this system is functioning or can be stimulated. Another serious complication in cancer chemotherapy is that many tumors are derived from a number of clones that differ in their drug sensitivity. Initial treatment can produce a remission by destroying the sensitive clones. Nevertheless, the resistant ones can ultimately regenerate the cancer. Combinations of drugs acting by different mechanisms have been developed to forestall the proliferation of resistant clones.

At the present time at least 10 neoplasms can be treated with good expectation of a cure: acute leukemia in children, Burkitt's lymphoma, choriocarcinoma, Ewing's sarcoma, Hodgkin's disease, lymphosarcoma, mycosis fungoides, rhabdomyosarcoma, retinoblastoma in children, and testicular carcinoma. These tumors tend to be the rarer ones. Unfortunately the outlook is not so good for patients with such common tumors as those of the liver, pancreas, colon, and lung. Breast cancer continues to be a serious cause of death, although progress is being made against it. Numerous other tumors give partial responses to chemotherapy, but the beneficial effect often is of short duration. Needless to say, chemotherapy is only one mode of cancer treatment. Surgery is the prime mode for solid tumors and radiation is used for skin cancer and localized deeper tumors. Even in these cases chemotherapy is used as an adjuvant, particularly when metasteses are suspected.

In this volume on antineoplastic drugs we have tried to describe the nature of cancer cells and to relate their special properties to the problem of developing chemotherapeutic agents. Chapter 1 describes cell division and the cell cycle. It considers in detail cell kinetics and stem-cell biology. Opportunities for drug specificity related to differences in these cell properties between cancer and normal cells are discussed. In Chapter 2 the screening systems used for the identification of potential anticancer drugs are described and evaluated for their predictive potential. *In vitro* and *in vivo* systems are considered and problems in correlating antitumor activity in tissue culture or animal screens with human clinical activity are explored. The third chapter is presented from the viewpoint of the medicinal chemist. It considers the large body of research devoted to understanding the chemical interaction of antitumor agents with biological targets such as DNA and enzymes and how investigators have tried to apply this knowledge to the rational design of improved agents. Studies of the preparation of analogs of natural and synthetic lead compounds are described, and recent efforts to place analog selection on a sounder basis by the use of quantitative structure-activity relationships are examined.

Our hope is that this volume will provide a guide and stimulus to chemists and pharmacologists active in or seeking to enter cancer research. Despite the difficulties of curing many types of cancer, progress is being made in all of the essential scientific areas, including tumor biology, screening methodology, drug design, and clinical evaluation. This is a time of rising expectations in the field.

WILLIAM A. REMERS

Tucson, Arizona
December 1983

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ONE

The Cellular Basis of Cancer Chemotherapy

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INTRODUCTION AND GENERAL PRINCIPLES

Cancer is a disease of cells characterized by the reduction or loss of effectiveness of the normal controlling influences that maintain cellular organization in tissues. Cancer cells have acquired properties that, in simplistic terms, provide them with growth advantages over normal cells; this permits their continuous proliferation not only in their sites of origin but also in other environments. The abnormal behavior of tumor cells leads to damage in the host at a variety of levels; (a) locally by pressure effects, (b) by destruction of involved tissues, both physically and in terms of normal function, and (c) by systemic effects secondary to the localized growths.

As an initiation point in the design of therapy and the understanding of cancer growth, comparisons at different levels have been made of tumor and normal equivalent tissue from which we can summarize the basic features of cancer cells:

1. Uncontrolled cell proliferation.
2. A lack of cellular differentiation features.
3. The ability to invade surrounding tissue.
4. The ability to metastasize (establish new focal growth in distant sites).

An understanding of the mechanisms that underlie these bahavioral characteristics is fundamental to the development of therapy to eradicate cancers. We are concerned in this chapter with those aspects of tumor and normal cell behavior that impact on the use of chemotherapeutic agents.

Cancer therapy with cytotoxic drugs has made enormous progress since the initial application of chemicals in the late 1940s when Farber prescribed methotrexate to treat childhood leukemia. In recent years the emphasis has been on the integration of chemotherapy with other treatment modalities; surgery, radiotherapy, and immunotherapy. It is now clear that chemotherapy's most effective role in solid tumors is as an adjuvant to initial therapy by surgical or radiotherapeutic procedures. This realization has come about through an understanding that failures of primary field therapy are due prin-

cipally to the existence of occult micrometastases not accessible to surgery or localized radiotherapy. Chemotherapy becomes critical to effective treatment because only systemic therapy can attack micrometastases.

The design of treatment regimens, which include chemotherapeutic drugs, has, in major part, advanced empirically; numerous experimental protocols have been designed, some of which have markedly improved prognosis for a few types of cancer (for a review see Carter et al., 1981); for example, chemotherapy is considered curative in choriocarcinoma in women, Burkitt's lymphoma, Wilm's tumor in children, certain testicular tumors, and childhood leukemia. Unfortunately, in the most common human tumors (colon, lung, breast) chemotherapy has not had a major impact; indications are, however, that significant advances in the treatment of these tumors will derive from increased sophistication in the use of adjuvant chemotherapy.

The most common rationale for the use of chemotherapy is control of the growth of tumor cell populations by cell-kill mechanisms. A major limitation to this approach is the nonselectivity of chemotherapeutic agents. The capacity to use the available cytotoxic agents to kill tumor cells is limited by the effect of these drugs on critical normal tissues; therefore treatment is often limited by cell-kill effects in bone marrow (anemia, thrombocytopenia, neutropenia, and immunodeficiency) and intestinal mucosa and by damage to a variety of other normal tissues (lung, heart, kidney, and brain). A major challenge to the chemotherapist remains the design of tumor-specific therapy. Because cell-kill effects are basically dose-dependent, theoretically a large enough dose of an anticancer agent could eradicate the tumor. This rationale will become reality only when a totally tumor-specific agent can be formulated.

One approach to this problem has been to design regimens that contain combinations of agents that might act synergistically on tumor cells but not on normal tissues (Capizzi et al., 1977). There are a few examples of such effects: the combination of cis-platinum, vinblastine and bleomycin in the treatment of testicular tumors (Einhorn, 1977) and methotrexate, 5-fluorouracil and cyclophosphamide (Canellos et al., 1976) in breast cancer. The combination of chemotherapeutic agents has been attempted rationally by combining agents with different mechanisms of action. A good example is the MOPP regimen (mustard, vincristine, procarbazine, and prednisone) used successfully in the treatment of advanced Hodgkin's disease (Devita et al., 1970).

Because the most obvious characteristic of tumor tissue is its increase in size by an increase in cell number, chemotherapeutic agents have naturally

been selected as antiproliferative. Their ability to impede cell proliferation is in general a function of interference with a critical biochemical component of the cell division process. The efficiency of interaction of drugs with tumor tissue is quite obviously dependent to a major degree on noncellular processes, which include pharmacokinetics, drug distribution in tumor and normal tissue, and drug effects on tumor architecture (connective tissue and vascularization). This chapter deals only with cellular effects; it must be acknowledged, however, that these effects may play a minor role in the overall determination of the outcome of chemotherapy.

To discuss adequately the cellular features of tumor and normal tissue that determine drug response it it necessary to compile information from a variety of scientific disciplines. It is beyond the scope of this chapter to provide a critical review of all the scientific areas of this question. I intend therefore to target my discussion to the theme of human tumor cell heterogeneity and its effect on chemotherapeutic outcome. It is my hope that the reader will be able to probe in more detail any particular discipline by use of the bibliography. It is apparent that our understanding of human tumor cell biology has relied heavily on experimentation in animal tumor systems. Wherever possible, however, this discussion emphasizes information on human tumors.

CELL DIVISION, CELL CYCLE, AND DRUG SELECTIVITY

Cancer research has long concentrated on the apparent uncontrolled growth of tumor tissue in relation to the normal equivalent. Study of cell proliferation, as the central process in this growth, has therefore been singled out as holding special importance to the cancer problem. Could differences be detected in the proliferative processes of normal and tumor cells that account for the growth advantages of tumor cells? Although this view does not seem likely now, an understanding of the biochemical events underlying cell division are, of course, fundamental to an understanding of chemotherapy.

The replicate characteristics of mammalian cells are conventionally described in terms of a cell cycle. This concept depends on the events between the birth of a new cell and its subsequent division as a series of ordered, unique biochemical events (Hill & Baserga, 1975; Mueller, 1971).

Morphologically, dividing mammalian cells exist in two basic states; one of actual cell division (mitosis) and a much longer interphase period. It has