to its alkylated homologs II and III is not obvious. It is hoped that subsequent work on benzoquinone biosynthesis in other arthropods may clarify this problem.

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Jerrold Meinwald, Kay F. Koch[11]
Joseph E. Rogers, Jr., Thomas Eisner
Department of Chemistry and Division of Biological Sciences
Cornell University, Ithaca, New York 14850
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Book Reviews

Advances in Chemotherapy. Volume 1. Edited by ABRAHAM GOLDIN, National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and F. HAWKING, National Institute for Medical Research, Mill Hill, London, England. Academic Press Inc., 111 Fifth Ave., New York, N. Y. 1964. xi + 579 pp. 15.5 × 23.5 cm. $17.50.

This book represents a remarkable achievement in fulfilling the goals which its editors had set for themselves: "to offer a common meeting ground for investigators in chemotherapy who may have come into this subject from organic chemistry, biochemistry, pharmacology, genetics, microbiology, parasitology, immunology, physiology, pathology, or other scientific disciplines." It accomplishes an excellent balance between theory, fundamental principles, and experimental findings in the field of chemotherapy which should appeal both to the experts, as well as to the "novices" in this area of drug therapy. It offers a dynamic view of drug interaction at the cellular level both in the host and the invading microorganism without sacrificing on the details of experimental evidence. While speculative in many instances as to the mode of action of chemotherapeutic agents, the authors, nevertheless, treat their own speculations with an air of detachment and a healthy amount of skepticism.

The introductory chapter by E. K. Marshall on "Historical Perspectives in Chemotherapy" sets the stage for this valuable treatise and brings the reader quickly up-to-date on past accomplishments in the rapidly growing areas of the chemical treatment of parasitic, viral, and neoplastic diseases. While this book is written by nine different authors, it does achieve a measure of cohesiveness seldom seen in works of this nature.

It is noteworthy that at the very outset the reader is apprized of the difficulties which beset the clinical investigator in selecting a candidate agent for clinical evaluation on the basis of biochemical, animal pharmacologic, and toxicologic data which may or may not be predictive of the ultimate activity and toxicity of the new drug in man. While this chapter by Zubrod on the "Quantitative Concepts in the Clinical Study of Drugs" is, of course, applicable to all types of therapeutic agents, it does point to the particular plight of the clinician dealing with the treatment of neoplastic diseases where drugs have to be administered at near toxic levels to produce a regression of the disease. The plea made by the author for clinical relevancy of toxicologic, biochemical, and pharmacologic test procedures is well taken, since all too often, animal methodology is developed with little attempt to simulating actual clinical conditions. The interdisciplinary approach to phases I and II in the clinical evaluation of a candidate agent receives particular emphasis. Continued surveillance of the new drug for several years once it has been "turned loose on the community" is strongly advocated by the author to establish an epidemiological pattern of side effects and toxicities in a given population.

Newton's chapter on the "Mechanism of Action of Phenanthridine and Aminoquinaldine Trypanocides" points to the complexities of combating trypanosomiasis which is influenced by climate, altitude, vegetation, and pattern of human migration. The disadvantages of the *Crithidia oncopelti* test system are discussed in the light of the differences of the drug effects in insect forms as compared to those obtained in the blood stream.

While little is known relative to the biochemistry and mechanism of action of the quinaldines and phenanthridines, the interaction of quinapyramine and homidium with various cellular systems is discussed. Quinpyramine changes the growth pattern of the trypanosome cell system from an exponential to a linear form. Hence, while this group of drugs is not trypanocidal, it reduces the trypanosome population sufficiently for the body's defenses to take over. The use of washed cell suspensions to study the effects of these drugs on nucleic acid and protein synthesis reveals that quinapyramine causes a progressive inhibition of RNA synthesis which may be reversed by *p*-aminobenzoic acid. The trypanocidal drug, homidium, on the other hand, inhibits the synthesis of DNA in the trypanosome cell. Failure of quinapyramine to inhibit DNA synthesis and glycine incorporation into nucleic acid is thought to be due to the inability of the drug to penetrate the cell nucleus. Evidence is presented which indicates that quinapyramine modifies the normal binding of ribosomal RNA to protein. The aggregation of ribosomes caused by the presence of the drug results in loss of their biological activity. C^{14} adenine incorporation into nucleic acids is inhibited by quinapyramine.

The effect of homidium and quinapyramine on other cell systems is discussed; *e.g.*, in Ehrlich's ascites tumors and *E. coli*, homidium is a potent inhibitor of purine incorporation into nucleic acids.

Speculations to explain the phenomenon of selective toxicity (damage to parasitic cell, but not to host cell) of these two groups of drugs are offered by the author.

Studies of the high degree of cross resistance between the various curative and prophylactic agents are complicated by the fact that it is difficult to obtain resistant strains in laboratory animals.

In bacteria, homidium is a potent inhibitor of protein and nucleic acid synthesis. Several of the phenanthridines also inhibit the development of the influenza virus in eggs.

The chapter by R. G. Thompson on the "Chemoprophylaxis and Chemotherapy of Viral Diseases" is a concise summary review of the various chemical structural types that have displayed antiviral activity *in vitro* and in intact animals. Of all these drug types, only 2′-dioxy-5-iodouridine (IUDR) has become commercially available for the treatment of keratitis produced by *Herpes simplex* and *vaccinia* virus. Both viruses contain only DNA; IUDR interferes with the synthesis of DNA and thereby inhibits replication. It has no activity on RNA containing viruses. Thompson points out that there are either DNA or RNA containing viruses and drugs normally active against one type of virus will usually be inactive on the other virus strain.

The role of interferon, an endogenous substance which is released by the body during viral infections, is discussed with respect to its action as a prophylactic agent and an inhibitor of virus production. It acts against both RNA and DNA containing viruses.

Two other drugs, cytosine arabinoside and isatin β-thiosemicarbazone, also display promising antiviral properties.

While at present, there can be little correlation between chemical structure and antiviral activity, the fact that a few of the synthetic

antiviral agents have displayed useful therapeutic properties in man holds out hope that the chemical treatment of viral disease is entirely feasible. If the mechanism of action is interference with nucleic acid synthesis, selectively acting agents must be developed which will not interfere with normal cell metabolism when administered systemically. Furthermore, such drugs must be capable of inhibiting virus production *after* the infection has started, since a mere prophylactic action is at best impractical from the therapeutic standpoint. The agent need not be virucidal but should check viral production until the body has been able to develop sufficient antibodies to produce an immunological response. A highly effective virucidal agent would prevent the development of immunity and leave the body defenseless against subsequent viral infections by the same virus, since resistance and cross resistance develop quite readily with many types of antiviral drugs. It is, therefore, desirable to allow a relatively high antibody titer to develop, thereby assuring the body of permanent or semipermanent protection against future infections by the same virus.

The synergistic effect of anti-inflammatory agents in enhancing the action of antiviral agents in animal is worthy of note, even though cortisone will exacerbate viral infections.

The chapter on "The Vinca Alkaloids" by Neuss, *et al.*, is a well-balanced treatise on this new group of antileukemic agents from the standpoint of covering the chemistry, pharmacology, antitumor, antiviral and clinical properties of this interesting class of alkaloids. Both vinblastine and vincristine have received extensive clinical trial, the former being active in chorioepithelioma, Hodgkin's disease, and other lymphomas and the latter inducing complete remissions in childhood leukemias. Although the two drugs are structurally related, there is no cross-resistance. Especially gratifying is the fact that laboratory testing methods were able to forecast the clinical therapeutic potential of these agents. What one misses in this chapter are follow-up studies regarding the duration of these remissions, particularly in the area of acute childhood leukemia. Presumably, such data were not yet available at the time this paper was written. This may also hold true in regard to the incidence of clinical side effects which these compounds may elicit during chronic administration.

The largest chapter in the book is devoted to "Cell Culture and Cancer Chemotherapy" by Foley and Epstein. It is a highly authoritative treatise which covers the details of experimental procedures of working with cell and organ cultures and clearly points out the potential scope of this technique for the study of drugs on a molecular level. It deals with such important topics as drug resistance, the nutritional and metabolic requirements for cellular growth which unfortunately appear to be quite similar for the normal mammalian and neoplastic cells, membrane permeability and its alteration by drugs, the role of RNA in cellular differentiation, the possible mechanism of action of Actinomycin in the therapy of lymphoma and Wilms tumor, the comparative merits of the mammalian cell culture, and other *in vitro* systems in drug evaluation and the measurement of drug sensitivity.

The experimental evidence presented by the authors supports their contention that there is a remarkably good correlation between drug-induced inhibitory activity in mammalian cell assays and experimental antitumor activity.

The technique of organ culture would appear to be a highly effective tool for determining the mechanism of action of many diverse drugs, their inherent toxicological properties, and their propensity for inducing teratological effects. One must agree with the authors that this valuable assay tool has certainly not received the attention it should in the study of the mechanism of drug action and drug toxicology.

The authors conclude that the mammalian cell assays satisfy the criteria required of a useful screening procedure in the search for potential antitumor agents.

In his chapter on "Immunoreactions in Antiparasitic Therapy," Goble makes a strong plea for the concept of the "eternal triangle" of the "drug–host–invader complex." The chemotherapy of infections, as the author rightly points out, must be regarded in terms of a triangular relationship between drug, parasite, and host, with the dependence of the ultimate therapeutic effect on the defense mechanism provided by the body. Thus, drugs are viewed as "adjuncts" to meet the emergency before the body is able to take over.

With this triad of a dynamic relationship, the author then proceeds with the discussion of the separate effects of each component: the action of the drug on the host and *vice versa*, the various effects of the chemotherapeutic agents on parasites and of the parasites on the drug, and the interaction of the host and parasite. With regard to protozoan infections, the following factors are considered: (a) species and age of animal in relation to drug efficacy, (b) therapeutic regimen in relation to drug efficacy and development of immunity, (c) the ability of a chemotherapeutic agent to induce antigenic variations, (d) chemotherapeutic agents as tools in the study of immunity, (e) the interference of certain steroids with the body's defense systems, (f) conditions which will avoid or suppress immunoreactions and thereby favor the development of drug resistance, (g) the mechanism of host cooperation in chemotherapeutic cure (the reticuloendothelial system must remain intact for the immunological response to occur), and (h) the prevention of the immunological response by too premature and too massive chemoprophylaxis. These principles are discussed further in relation to the treatment of malaria, trypanosomiasis, and coccidiosis.

The chapter on "Drug Synergism in Antineoplastic Chemotherapy" by Venditti and Goldin strikes, of course, at the heart of cancer chemotherapy. The goals of multiple drug therapy are: (a) the lowering of toxicity, (b) the increase in efficacy and survival time, and (c) the prevention of drug resistance.

The various obstacles which the host presents to successful chemotherapy are discussed, such as the physiological barriers to the penetration of the drug to the target organ, the physiologic disposition (premature binding of drug at sites other than the target organ), biotransformation of the drug (some drugs will accelerate their own metabolism on chronic administration), and the too rapid excretion of the drug. All of these factors indicate the need for the addition of chemical agents which can overcome the disadvantages of single drug therapy. Several examples of such drug synergism are described by the authors including internal structural changes of an active drug by incorporating "transporting"moieties, such as phenylalanine, in the nitrogen mustards which increase survival time of mice with Sarcoma 37 several fold.

The discussion of the biochemical basis for drug synergism and drug resistance forms an integral part of this chapter. The authors conclude with the statement that thus far no dramatically active drug combination has been discovered in cancer chemotherapy.

The most challenging chapter from the standpoint of presenting new vistas in chemotherapy is by Kaplan and Friedkin on "New Concepts of the Use of Inhibitors in Chemotherapy." This chapter should be of particular interest to the medicinal chemist working in the field of chemotherapeutics.

The concept of "feedback" or end-product inhibition is a rather fascinating departure from the classical antimetabolite approach. The administration of the terminal metabolite in an enzymatic reaction sequence may produce a powerful block to the first enzyme reaction in the sequence. In the same vein, the administration of an inhibitor of the biotransformation of the terminal metabolite would produce an accumulation of this metabolite and, thereby, initiate a negative feedback and blockade of the first reaction step in the enzymatic reaction sequence.

In the light of this concept of "allosteric inhibition," the authors discuss many of the important enzyme systems in the body which would lend themselves to such an approach and would form the basis for rational drug design.

Another biochemical concept suggested by the authors is the "redirecting" of cellular metabolic pathways by genetic control. Such new pathways might be more susceptible to chemotherapy.

The interference with messenger RNA synthesis by Actinomycin D is due to the specific formation of an unusual Actinomycin–DNA complex which results in the inhibition of RNA synthesis. The authors feel that such a mechanism may have "implications of vast importance, since the synthesis of enzymes is the dynamic expression of genetic information residing in RNA and DNA."

John H. Biel
Research Department, Aldrich Chemical Company
Milwaukee, Wisconsin 53210

The Chemistry of the Antibiotics used in Medicine. By R. M. Evans, D.Sc., D.I.C., F.R.I.C., Glaxo Research Limited, Greenford, Middlesex. Pergamon Press Inc., 44-01 21st St., Long Island City, N. Y. 1965. x + 226 pp. 13 × 19.5 cm. 25s.

While it is proper that many volumes and monographs should be concerned with the medical uses, biological activities, and methods of production of the antibiotics, it is pleasant to find this small volume which concerns itself with the *chemistry* of these substances. As its title indicates, it encompasses primarily those antibiotics which have found use in clinical medicine. But by discussing