ADVANCES IN DRUG RESEARCH

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Edited by

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PREFACE: TEXT AND CONTEXT

No research paper is adequately communicative and informative without an introductory part outlining the scientific context of the reported work, and a conclusion placing its findings in a broader context. Many of us certainly remember trying to grasp the meaning and significance of publications which, due to lack of explicit introduction and conclusion, should best be considered as technical reports written for the benefit of insiders. In other words, research papers are meaningful only within the frame of their scientific context.

Major review articles such as the chapters featured in this volume differ from research papers by more than their length and type of content. By definition, the contextual frame of reviews is much broader than that of research papers since they summarize findings and concepts originally presented in a number of original publications. Yet the essential difference lies elsewhere. By integrating many findings and concepts, reviews enlarge and explicate the scientific context of research papers both recent and future. Reviews as well as books are thus *context makers*, and as such fulfil a function essential to the advance of science.

These thoughts occurred to me while reading the scientific testament of Gregory Bateson (1980), a book in which this great anthropologist and epistemologist offers some enlightening sentences about context (or "pattern through time"), about "contexts which confer meaning because there is classification of contexts", and about "patterns which connect patterns".

To integrate the contexts of innumerable studies, and to offer a higher-order context giving sense and import to current research efforts, such are the goals and achievements of the texts making up this volume. Different as they may be in form and content, all five chapters have necessitated considerable dedication from their authors, as well as a readiness to fit into the approach and wise by which *Advances in Drug Research* in turn aim at becoming a "pattern connecting patterns".

The volume opens with two chapters dealing with chemotherapeutic agents, continues with a more general chapter on drug receptors in the cardiovascular system, and closes with two neuropharmacological chapters. The first chapter by De Clercq is an account of the latest findings in the search for selective antiviral agents. As one of the best world experts in this fast expanding field, De Clercq has prepared a text that is both highly readable and systematic, rationalizing present data and pointing to directions for future research. The second chapter covers recent developments in

the field of cephems, a group of β-lactam antibiotics which is attracting much attention. It is the merit of Dürckheimer and colleagues to combine the synthetic chemistry, structure–activity relationships and disposition of cephem antibiotics into an encyclopaedic treatment which may well remain unequalled for many years.

These two chapters are followed by a monumental work on the cardiovascular system and its receptor regulations, a jigsaw puzzle whose complexity defies our understanding. The chapter by Ruffolo and Nichols reviews the pieces of the puzzle with clarity and depth only to transcend the analytical level and render this complexity discernible to the reader. This is followed by a short and dense chapter on serotonin receptor agonists and antagonists in which Fuller summarizes recent breakthroughs and critically evaluates some of their therapeutic potentials.

The last chapter by Krogsgaard-Larsen and co-workers is another testimony to scientific achievement and communicative skill. This team has successfully pioneered synthetic and pharmacological research on GABA agonists, antagonists and uptake inhibitors, and here offers a text of particular richness and impact.

Editing this volume has been a lasting source of fun and much enrichment. May the same feeling be felt by the reader, with whom the contributors share their knowledge, insight and enthusiasm. It was the inspired Bateson again who wrote that "at present, there is no existing science whose special interest is the combining of pieces of information" (Bateson, 1980). This statement is certainly valid, yet we may wonder whether the writing and study of texts such as those offered here are not endeavours pregnant with the unborn science of context making.

BERNARD TESTA

Reference

Bateson, G. (1980). "Mind and Nature—A Necessary Unity". Fontana Paperbacks, London.

CONTENTS

Recent Advances in the Search for Selective Antiviral Agents

E. DE CLERCQ

Recent Developments in the Field of Cephem Antibiotics

W. DÜRCKHEIMER, F. ADAM, G. FISCHER AND R. KIRRSTETTER

Recent Experimental and Conceptual Advances in Drug Receptor Research in the Cardiovascular System

R. R. RUFFOLO, JR. AND A. J. NICHOLS

The Pharmacology and Therapeutic Potential of Serotonin Receptor Agonists and Antagonists

R. W. FULLER

Recent Advances in GABA Agonists, Antagonists and Uptake Inhibitors: Structure–Activity Relationships and Therapeutic Potential

P. KROGSGAARD-LARSEN, H. HJEDS, E. FALCH, F. S. JØRGENSEN AND L. NIELSEN

Recent Advances in the Search for Selective Antiviral Agents

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1 Introduction

Antiviral chemotherapy has now definitely come of age. While almost 25 years have elapsed since the first antiviral agent (idoxuridine, IDU, 5-iodo-2′-deoxyuridine) was marketed, the clinical use of antiviral agents has gained renewed interest due to the successful introduction of acyclovir [ACV, 9-(2-hydroxyethoxymethyl)guanine] in medical practice (De Clercq, 1988a). The search for new antiviral agents has been further boosted by the advent of AIDS (acquired immune deficiency syndrome) and the identification of a retrovirus, now termed human immunodeficiency virus (HIV), as the causative agent of the disease. For recent reviews on the subject of antiviral chemotherapy, see Dolin (1985), De Clercq (1985a, 1986a,

ADVANCES IN DRUG RESEARCH, VOL. 17
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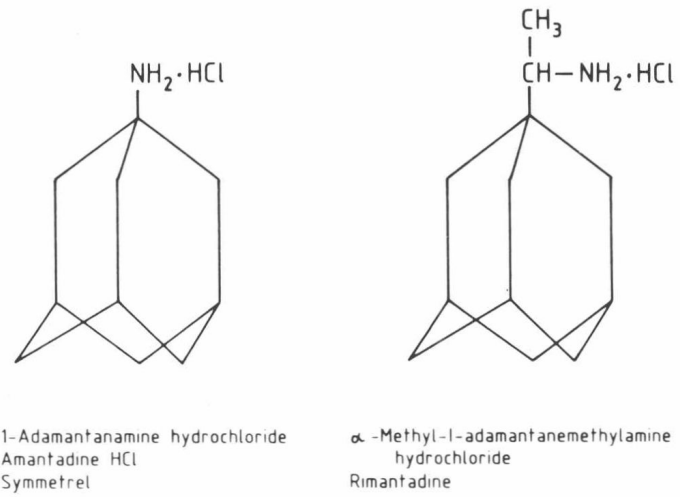


FIG. 1. Amantadine and rimantadine.

1987b,c,d,e) and De Clercq and Walker (1986). The current armamentarium of antiviral drugs which have been licensed for clinical use consists of amantadine, rimantadine (Fig. 1), idoxuridine, trifluridine (Fig. 2), vidarabine (Fig. 3), acyclovir (Fig. 4), ribavirin (Fig. 5) and retrovir (Fig. 6). Amantadine and rimantadine are useful in the prophylaxis and early therapy of influenza A virus infections. Idoxuridine, trifluridine, vidarabine and acyclovir are used in the topical treatment of herpetic keratitis. Acyclovir is used for the systemic (intravenous or peroral) treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections. ACV is particularly useful in the treatment of primary genital herpes and herpetic encephalitis, where it is superior to vidarabine. ACV can also be recommended for the prophylaxis of recurrent genital herpes, the therapy and prophylaxis of HSV infections in immunosuppressed patients and the treatment of VZV infections in immunosuppressed patients, where again it is superior to vidarabine. Ribavirin has been licensed for topical (aerosol) treatment of respiratory syncytial virus (RSV) infection in infants, and retrovir has recently become available for the treatment of patients with AIDS and ARC (AIDS-related complex).

While the availability of some antiviral compounds for some virus infections by no means suggests that no further search towards new and more potent or selective drugs for these diseases is warranted, there are many other viral diseases that are in great need of an effective antiviral

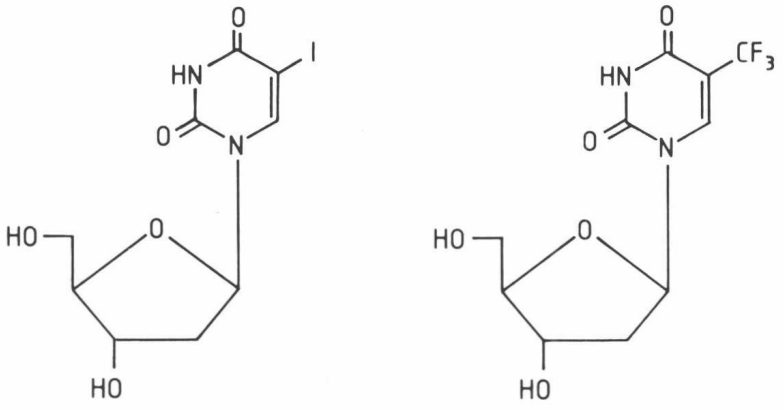


FIG. 2. Idoxuridine and trifluridine.

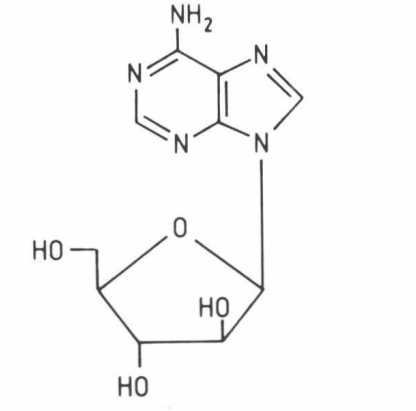
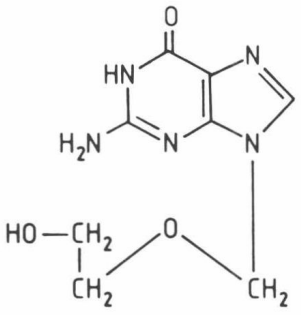
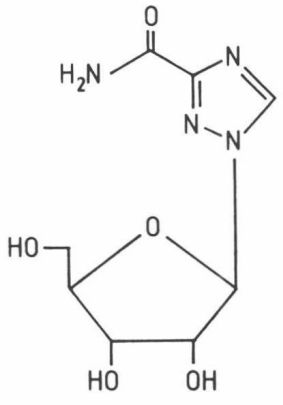


FIG. 3. Vidarabine.



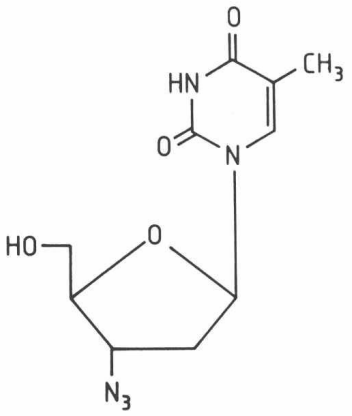
9-(2-Hydroxyethoxymethyl)guanine
Acycloguanosine
Acyclovir, aciclovir (ACV)
Zovirax

FIG. 4. Acyclovir.



1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide
Ribavirin
Virazole

FIG. 5. Ribavirin.



3'-Azido-2', 3'- dideoxythymidine (AzddThd)
Azidothymidine (AZT)
Retrovir
Zidovudine

FIG. 6. Retrovir.

chemotherapy. These include, among others, the members of the herpesvirus family, such as cytomegalovirus (CMV), which often leads to life-threatening complications in immunosuppressed patients, and Epstein-Barr virus (EBV), which is associated with various B-cell lymphoproliferative disorders; adenovirus infections, which again may be occasionally fatal in immunocompromised patients; papillomaviruses which are etiologically linked to warts, condylomata acuminata, genital carcinomas and other malignant tumours; rhinoviruses and other respiratory tract viruses, which can be considered as the infectious pathogens with the greatest socioeconomic impact; rotaviruses, which have been recognized as the single most important causative agents of acute diarrhoea, which, in turn, ranks among the leading causes of morbidity and mortality in infants and young children, particularly in developing countries; haemorrhagic fever viruses (i.e. Lassa, Junin, Machupo, Rift Valley) which rank among the most deadly pathogens, and, although confined to some areas of the world, are difficult to control by vaccination; and hepatitis B virus, which counts 200 million carriers in the world of which 40 million may die from cirrhosis and another 10 million from hepatocarcinoma (Hilleman, 1987).

It is clear, therefore, that the need for treatment of viral diseases has remained enormous, as the currently available drugs barely scratch the surface (Galasso, 1988). Science, politics and public apprehension about

AIDS have fuelled antiviral drug development, and the resulting burst of efforts has already generated a wealth of compounds which hold promise for the treatment of AIDS. This momentum in antiviral research should not only be nurtured and maintained, but accelerated and expanded to other viral diseases in urgent need of antivirals.

2 Herpesvirus Infections

2.1 ACYCLOVIR

Acyclovir (Fig. 4) has acquired an established position in the chemotherapy of HSV infections (Table 1). Oral acyclovir is the treatment of choice for first episodes of genital herpes (Mindel *et al.*, 1987); it is of slight benefit in the treatment of recurrent genital herpes, but when given prophylactically it prevents reactivation of symptomatic recurrences of genital herpes (Straus

TABLE 1

Major indications for the clinical use of acyclovir

Dosage (duration)	Route of administration[a]	Indication
		Therapy
3% eye ointment	top.	Herpetic keratitis
5% cream or ointment (up to 10 days)	top.	Primary genital herpes
15 mg/kg/day (5–10 days)	p.o., i.v.	Primary genital herpes
15 mg/kg/day (7 days)	i.v., p.o.	HSV infection in immuno-compromised patients
30 mg/kg/day (10 days)	i.v.	Herpes simplex encephalitis
30mg/kg/day (7 days)	i.v.	Varicella or zoster in immuno-compromised patients
15–30 mg/kg/day	i.v.	Neonatal herpes
60 mg/kg/day (7 days)	p.o.	Zoster
		Prophylaxis
15 mg/kg/day	p.o.	HSV infection in bone marrow transplant recipients
		Recurrent genital herpes

[a] Top., topically; p.o., perorally; i.v., intravenously.

et al., 1984). For the latter indication the use of acyclovir is at present limited to a 6-month course in patients with frequent recurrences (Corey and Spear, 1986). In immunosuppressed patients with mucocutaneous HSV infections, intravenous or oral acyclovir relieves pain and accelerates healing of both symptomatic first and recurrent episodes, and, in addition, intravenous or oral acyclovir taken daily prevents recurrences during high-risk periods, i.e. immediately after bone marrow transplantation. In the treatment of recurrent herpes labialis, topical acyclovir (5% cream) is of no clinical benefit (Shaw *et al.*, 1985), and oral acyclovir has not been studied. In the treatment of herpes simplex encephalitis, acyclovir is clearly superior to vidarabine (Sköldenberg *et al.*, 1984; Whitley *et al.*, 1986). Acyclovir is also superior to vidarabine in the treatment of VZV infections in immunocompromised patients (Shepp *et al.*, 1986). For acyclovir to afford a beneficial effect in the treatment of varicella or zoster, it has to be administered at higher doses than for the treatment of HSV infections, i.e. 2 g/day i.v., or even 4 g/day p.o. (Kendrick *et al.*, 1986). Only with an oral dosage regimen of 0.8 g acyclovir 4-hourly are mean steady state peak and trough plasma drug concentrations achieved that are in excess of the median effective dose for most VZV strains (Kendrick *et al.*, 1986). The clinical usefulness of acyclovir is limited to HSV and VZV infections. It is of little, if any, avail in the treatment of CMV infections, and, although acyclovir inhibits oropharyngeal excretion of EBV in patients with acute infectious mononucleosis (Ernberg and Andersson, 1986), it remains to be seen whether this reduction in virus burden is reflected by an alleviation of the clinical symptoms.

The mechanism of action of acyclovir (Fig. 7) is fairly well established. The compound is preferentially recognized as substrate by the virus-induced 2′-deoxythymidine (dThd) kinase (Fyfe *et al.*, 1978). It is actually the 2′-deoxycytidine (dCyd) kinase activity associated with the viral dThd kinase which is responsible for the phosphorylation of acyclovir to its monophosphate (De Clercq, 1982). Acyclovir monophosphate (ACVMP) is then phosphorylated by the cellular GMP kinase (Miller and Miller, 1980) to acyclovir diphosphate (ACVDP), which in turn is phosphorylated to acyclovir triphosphate (ACVTP) by nucleoside diphosphate kinase or other cellular enzymes (Miller and Miller, 1982). The antivirally active form of acyclovir corresponds to its triphosphate. ACVTP is strongly inhibitory to HSV DNA polymerase and, to a lesser extent, cellular DNA polymerases (Furman *et al.*, 1979; St. Clair *et al.*, 1980) and this inhibition is competitive with respect to the natural substrate dGTP; but, in addition, ACVTP can also be incorporated into DNA at its 3′-terminal, and, as the 3′-terminal ACVMP residues cannot be excised by the DNA polymerase-associated 3′,5′-exonuclease (Derse *et al.*, 1981), they prevent further chain elongation and thus act as DNA chain terminators. This explains the occurrence of

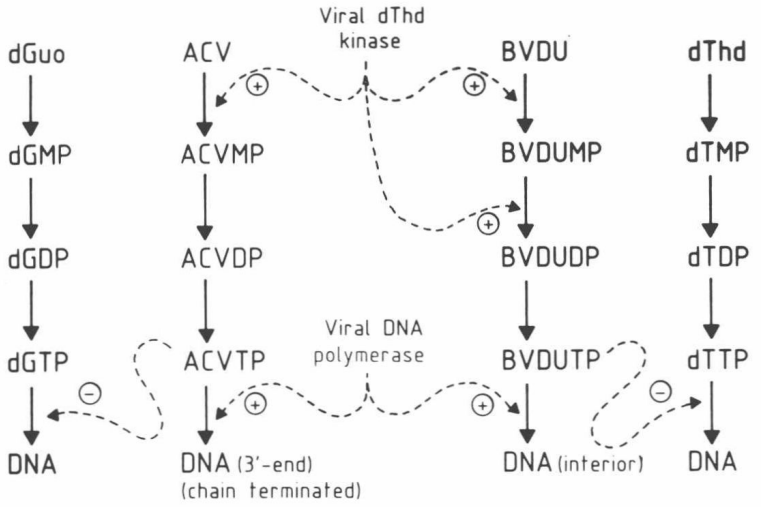


FIG. 7. Mechanism of action of acyclovir (ACV) and bromovinyldeoxyuridine (BVDU) against herpes simplex virus (HSV).

short DNA fragments in HSV-infected cells exposed to acyclovir (McGuirt *et al.*, 1984).

2.2 ACYCLOVIR DERIVATIVES

Acyclovir suffers from a number of drawbacks such as (i) poor solubility in water (about 0.2% at 25°C), (ii) low oral absorption (about 20% following administration of 200 mg) and (iii) limited activity spectrum, essentially confined to HSV and VZV and excluding such important pathogens as CMV. Because of its poor aqueous solubility, acyclovir cannot be given as eyedrops in the topical treatment of herpetic keratitis, or as intramuscular injections in the systemic treatment of HSV and VZV infections. To overcome this problem, water-soluble esters of acyclovir, i.e. *2′-O-glycylacyclovir* (Fig. 8), have been prepared (Colla *et al.*, 1983); and 2′-O-glycylacyclovir has proved efficacious in the treatment of herpetic keratitis when administered as a 1% eyedrop formulation to rabbits (Maudgal *et al.*, 1984). Attempts to find a prodrug of acyclovir which would be better absorbed after oral administration yielded *6-deoxyacyclovir* (Fig. 9). 6-Deoxyacyclovir is readily absorbed when administered p.o. and extensively converted to acyclovir by xanthine oxidase (Krenitsky *et al.*, 1984). Acyclovir concentrations achieved in the plasma following oral administration of 50 mg 6-deoxyacyclovir are comparable to those produced after