Progress in Drug Research

Fortschritte der Arzneimittelforschung

Progrès des recherches pharmaceutiques

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Ernst Jucker

31

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Contents · Inhalt · Sommaire

Foreword

Volume 31 of "Progress in Drug Research" contains 13 articles, a subject index, an index for all articles that have been published so far in this series of monographs, as well as an author and subject index for all 31 volumes. The reviews in this volume are particularly concerned with the therapy of helminth diseases, with pyramidinones as biodynamic agents, and with quinolones which are of interest in the treatment of infections. For a deeper understanding of the pharmacokinetic actions of modern drugs, the articles on cooperative binding of drug molecules to DNA, on in vitro models for the study of antibiotic activities, on inhibitors of the renin-angiotensin system, on GABA-drug interactions, and on the mechanism of action of anxiolytic drugs provide a wealth of facts and new findings. The pharmacology of caffeine is reviewed from the viewpoint of its role in combination with other physiologically active substances, and the chapter on high resolution nuclear magnetic resonance spectroscopy demonstrates the importance of this method in the development of new drugs. Finally, the article on light and dark touches border problems of the therapy of psychic disorders.

With these contributions, the authors aim to summarize latest achievements in important and actual fields of drug research. Researchers who are actively engaged in the same or in similar fields of research are sure to benefit from these efforts. For others, the reviews present an opportunity to get acquainted and to keep abreast with the latest developments and progress in the complex and heterogeneous domaine of drug research. The 31 volumes of "Progress in Drug Research" contain more than 300 reviews with innumerable references to the relevant literature, thus providing the reader with an almost encyclopedic source of information.

I should like to thank all the authors who willingly shared their vast knowledge and experience with the readers of these monographs. Thanks are also due to Professor Urs Meyer who contributed to this volume by inviting some of the authors to provide interesting articles. The work of the editor was, as usually, greatly facilitated by the help and expertise of Mr. H.-P. Thür and A. Gomm from Birkhäuser Publishers; I extend my sincere thanks to both of them.

Basel, October 1987 Dr. E. JUCKER

Vorwort

Der 31. Band der Reihe »Fortschritte der Arzneimittelforschung« enthält 13 Beiträge mit einem Stichwortverzeichnis des Bandes sowie je ein Verzeichnis aller bisher publizierten Artikel und aller Autoren mit ihren Beiträgen der 31 Bände.

Die Referate des vorliegenden Bandes decken wiederum ein weites Gebiet der Arzneimittelforschung ab: Therapie der Wurmkrankheiten, Pyrimidinone mit biodynamischen Wirkungen und Chinolone mit bakteriziden Eigenschaften sind in den drei spezifisch auf Wirkungen und Substanzgruppen ausgerichteten Artikeln behandelt. Die Beiträge über die kooperative Bindung von Wirkstoffmolekülen an DNA, die in vitro Modelle zum Studium der antibiotischen Wirkung, Inhibitoren des Renin-Angiotensin-Systems, GABA-Wirkstoff-Wechselwirkung und Wirkungs-Mechanismus von anxiolytischen Wirkstoffen vermitteln eine Fülle von Tatsachen und neuen Befunden, die für das bessere Verständnis der pharmakokinetischen Eigenschaften moderner Arzneistoffe unerläßlich sind. Die Pharmakologie des Coffeins wird vom Standpunkt seiner Verwendung in Kombination mit anderen Wirkstoffen dargestellt, und der Artikel über die Spektroskopie beleuchtet die Bedeutung dieser modernen physikalischen Methode bei der Entwicklung neuer Arzneimittel. Der Beitrag über Licht und Dunkel als Arznei vertieft unser Wissen in einem interessanten Randgebiet der Therapie psychischer Erkrankungen.

Mit diesen Beiträgen haben die Autoren einige der neuesten Entwicklungen im Gebiet der Arzneimittelforschung dargestellt, und die vermittelten Erkenntnisse und Befunde können den in diesen Gebieten tätigen Forschern eine wertvolle Unterstützung ihrer Untersuchungen bedeuten. Der nicht unmittelbar involvierte Forscher erhält dank der knappen und übersichtlichen Darstellung der Materie ein Hilfsmittel zur Aufrechterhaltung des Kontaktes mit verschiedenen Gebieten der komplexen und heterogenen Arzneimittelforschung. Die 31 Bände der Reihe mit den mehr als 300 Übersichtsreferaten und den unzähligen Literaturhinweisen stellen auch ein Nachschlagewerk von enzyklopädischem Charakter dar.

Das Erscheinen dieses 31. Bandes der «Arzneimittelforschung» möchte ich zum Anlaß nehmen, den Autoren dafür zu danken, daß sie ihr

Wissen und ihre Erfahrung uneigennützig dem Leserkreis dieser Reihe zur Verfügung gestellt haben. Auch sei Professor Urs Meyer der Dank für seine Mitarbeit an diesem Band ausgesprochen; er hat mit seiner Einladung einzelner Autoren dazu beigetragen, daß der Umfang dieses Bandes durch verschiedene interessante Beiträge erweitert wurde. Ganz besonders möchte ich aber dem Birkhäuser Verlag, und insbesondere den Herren H.-P. Thür und A. Gomm, für ihre stete Unterstützung der herausgeberischen Tätigkeit danken.

Basel, im Oktober 1987 Dr. E. JUCKER

Treatment of helminth diseases – challenges and achievements[1]

By Satyavan Sharma
Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

[1] Communication No. 3816 from Central Drug Research Institute, Lucknow 226 001, India

1 Introduction

Among a large variety of parasitic diseases caused by the invasion of the human body by a number of bacteria, fungi, viruses, protozoa and helminths, the helminth infections undoubtedly constitute a major medical and public health problem all over the tropical and subtropical regions of the world. Despite significant advances made in the treatment of helminth diseases, the rate of incidence of these infestations has not satisfactorily declined. This is primarily because these are basically the diseases of poor masses where inappropriate sanitation, low living standards, and lack of health education along with ideal environmental conditions for the survival and replication of the parasites facilitate the dissemination of infections. Another major reason for the wide spread of helminthiasis is that, earlier, it was not considered to be involved with higher risks of morbidity and mortality, and hence, was unable to draw the attention of medicinal chemists, parasitologists and medical and health personnel. However it was soon realized that the high worm burden on the population is not only responsible for several grave clinical complications but also greatly hampers the socio-economic growth of the tropics by causing malnutrition and physical disability which finally leads to decreased working capacity in the people carrying helminth parasites. Furthermore, the presence of helminths in domestic animals induces less production of milk, fat, meat and wool, and thus, influences the economy of agricultural and dairy countries of the world.

The economic loss incurred by the helminth infections has also been estimated by various workers. According to an early estimate, Japan suffered an economic loss of US $ 60 million per year from hookworm infections alone [1]. The treatment of hookworm patients would have cost US $ 7 million which was only 11.7 % of the calculated loss. It has also been found that the hookworm *A. duodenale* sucks 0.15–0.23 ml of blood per day [2]. Thus the total blood loss for 1 million patients with an average of 100 hookworms would be 15,000 liters per day. Another human hookworm, *Necator americanus,* sucks 0.03 ml of the blood from its host. The total blood loss for 1 million people carrying an average of 400 worms would be 12,000 liters per day.

Similarly, ascariasis, a disease, earlier considered of no public health importance, has now been shown to cause malabsorption of macronutrients and vitamin A which leads to poor growth and protein caloric

malnutrition in children. This clinical manifestation has been observed by Stephenson and co-workers [3] in several preschool Kenyan children. In fact, in 1976, Kenyans lost 23.352 million calories or 2.35 million kg of food costing $ 4,400,000. The total loss due to ascariasis in Kenya was more than US $ 5 million which could have been prevented by the use of a broad-spectrum anthelmintic costing only US $ 1 million.

Ascariasis also leads to considerable carbohydrate depletion in patients. It has been estimated that a patient with 20 *Ascaris* worms may loose 2.8 g of carbohydrates daily [4]. This would amount to a 2,800 kg carbohydrate loss per 1 million patients daily. Ascariasis exerts a similar effect in animals too. Thus a pig with 20 *Ascaris* showed weight gain of 0.2 kg as compared to 0.4 kg in the case of uninfected control ones [5]. In a recent study it has been shown that pigs infected with *Ascaris* and on a low protein diet consumed 6.8 kg of food to gain 1 kg while the control pigs needed only 3.3 kg of the food to gain 1 kg of weight [6].

Urquhart [7] has estimated that the potential loss due to untreated parasitoses in ruminants would be £ 160 million. This was reduced to an actual loss of £ 30 million by treating the ruminants with anthelmintics costing only about £ 20,000. Similarly, in Florida, USA, losses may exceed US $ 500,000 annually due to liver fluke infection in cattle [8]. The total economic loss due to uncontrolled parasitic infection in livestock in USA has been estimated to be more than US $ 3 billion per year [9].

The helminth diseases in man and animals are caused by three groups of parasites belonging to the nematodes, cestodes and trematodes. The author has tried to present a concise and up-to-date account of the progress made in the treatment of various diseases caused by helminth parasites in the limited space of this article. It must be emphasized that this review is by no means the complete compilation of all the publications in this area, and, therefore, authors interested in a more detail treatise of the chemotherapy of helminthiasis are advised to consult some of the excellent texts [10–17]. The drug development aspects of nematode [18–29], cestode [30–35] and trematode [36–40] diseases have also been reviewed extensively.

2 Helminthiasis of the gastrointestinal tract

The gastrointestinal tract of man is the most common seat of predilection for a number of helminth parasites. Table 1 gives the general characteristics of the intestinal-dwelling helminths. The intestinal helminth infestations are usually acquired by ingestion of helminth eggs through food, drinks and soiled hands or by penetration of the infective larvae through skin. That is why this form of parasitic disease is prevalent primarily in the poor masses of the third world. However, scattered incidence of enteric helminthiasis has been reported from all over the world.

The intestinal nematodes using mouth as their portal of entry operate a simpler life cycle than those that enter the human body through skin (fig. 1). Some helminths such as the tapeworms use cows, pigs and

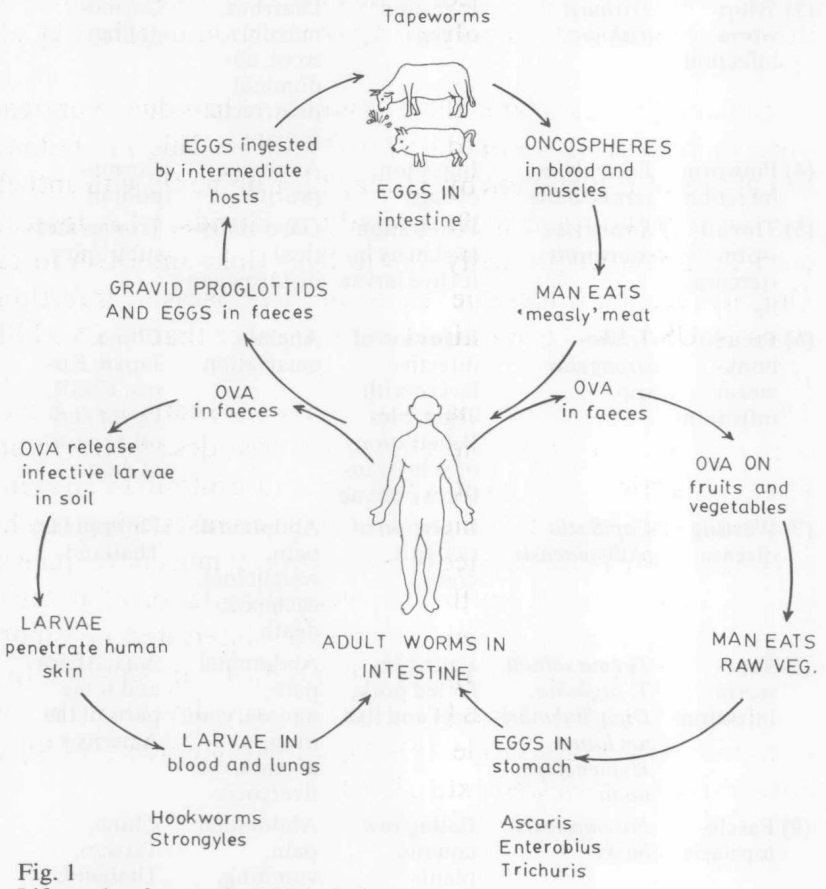


Fig. 1
Life cycle of some G. I. Helminths

Table 1
General characteristics of intestinal helminths.

Disease	Causative agent	Mode of infection	Main clinical characteristics	Geographical distribution	Population infected (in millions)
(1) Roundworm infection	*Ascaris lumbricoides*	Ingestion of eggs	Abdominal pain, intestinal obstruction, carbohydrate depletion	Worldwide	1,000
(2) Hookworm infection	*Necator americanus, Ancylostoma duodenale*	Penetration of skin by infective larvae	Anemia, malnutrition, weakness, epigastric discomfort	Asia, Southern Europe, Africa, South America, USA	800
(3) Whipworm infection	*Trichuris trichiura*	Ingestion of eggs	Diarrhea, mucoid stool, abdominal pain, rectal prolaps	Cosmopolitan	500
(4) Pinworm infection	*Enterobius vermicularis*	Ingestion of eggs	Anorexia, pruritis	Cosmopolitan	500
(5) Threadworm stercoralis	*Strongylus stercoralis*	Penetration of skin by infective larvae	Gastrointestinal disturbances	Tropics and subtropics	80
(6) Pseudohookworm infection	*Trichostrongylus* spp.	Ingestion of infective larvae with vegetables Penetration of skin by infective larvae	Anemia, emaciation	China, Japan, Korea, USSR, Egypt and other parts of Asia	10
(7) Wasting disease	*Capillaria philippinensis*	Ingestion of raw fish, crabs	Abdominal pain, weight loss, cachexia, death	Philippines, Thailand	0.003
(8) Tapeworm infection	*Taenia solium, T. saginata, Diphyllobothrium latum, Hymenolepis nana*	Eating infected pork, beef and fish	Abdominal pain, nausea, vomiting, anemia, cysticercocis	Asia, Africa and some parts of the Americas	82
(9) Fasciolopsiasis	*Fasciopsiasis buski*	Eating raw aquatic plants	Abdominal pain, vomiting, nausea, cachexia	China, Taiwan, Thailand, Burma, India, Laos, etc.	2

fishes as their intermediate hosts. They reach the gastrointestinal tract when man consumes poorly cooked beef, pork and fish products. The adult worms live in the intestine while their larval stages or bladder worms *(Cysticercus cellulosae, Cysticercus bovis)* migrate into the muscles.

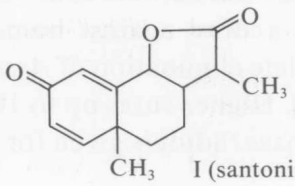
2.1 Treatment of ascariasis

2.1.1 Natural products

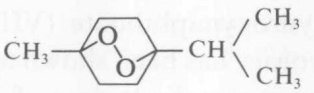
Santonin (I), a bitter tasting sesquiterpene isolated from the genus *Artemisia,* has long been used to treat human ascariasis. A dose of 200 mg per adult and 100 mg per child given either in gelatin capsules or with a sweet vehicle for 2–3 days causes elimination of the worms. The drug is generally well tolerated but may occasionally lead to kidney irritation, gastrointestinal disturbances, giddiness, epileptic-type convulsions and sensory or visual disturbances.

Ascardiol (II) is a terpene peroxide forming 60 % of the oil of chenopodium obtained from Jerusalem Oak *(Chenopodium ambrosioides).* The drug shows high activity against *Ascaris* in man when given at a dose of 200–300 mg in an empty stomach followed by a saline purge. A synergistic mixture of II and tetrachloroethylene ($Cl_2C=CCl_2$) in the ratio of 1:6 has been recommended for treating ascariasis and oxyurid infections in man.

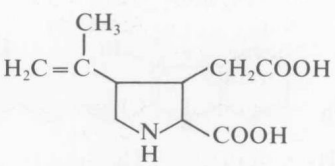
Kainic acid (III), isolated from red algae, *Digena simplex,* has been used in Japan for a long time to treat various nematode infestations in man. It is a non-toxic drug which shows better activity when given in combination with santonin (I) and piperazine (IV) [41, 42].



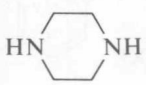
I (santonin)



II (ascaridol)



III (kainic acid)



IV (piperazine)

2.1.2 Piperazines

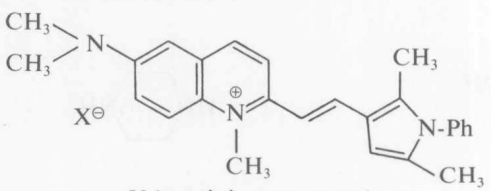
Piperazine (IV) is one of the most widely used drugs for treating ascariasis and other intestinal nematode infestations in man. A dose of 3.5–4.5 g/adult or at 50–75 mg/kg of piperazine base given in the form of its citrate, phosphate or adipate salts as tablets or in a syrup for 1–2 days causes almost 100 % cures with practically no side effects [20, 43]. However, occasionally, nausea, vomiting, diarrhea, abdominal discomfort and some allergic reactions may be observed in some treated patients.

Several combinations of piperazine have also been successfully used to treat various forms of enteric nematode infections in man [44]. Thus a mixture of piperazine with senna extract, pyrvinium pamoate (V) [45] or tetrachloroethylene [46] have been used to achieve high cure rates both against *Ascaris* and hookworm infections in man.

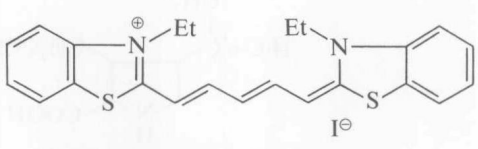
2.1.3 Quaternary ammonium salts

Dithiazanine iodide (VI) gives 65–100 % cures against human ascariasis at a dose of 40 mg/kg or 400–600 mg in one dose given for 2–5 days [47, 48]. The drug also gives rise to several toxic manifestations like nausea, vomiting, abdominal pain, diarrhea, fever, dizziness and albuminuria in the majority of treated cases. Some fatal cases of poisoning have also been reported [11].

Stilbazium iodide (VII) also exhibits high efficacy against *A. lumbricoides* in adults and children at a dose of 8–10 mg/kg given 1–3 times daily for 3 days [49]. Another quaternary ammonium salt, bephenium hydroxynaphthoate (VIII), primarily a drug against human hookworms, has been shown to cause complete elimination of *Ascaris* when given at a single dose of 2.5 g base [50]. Higher cures up to 100 % may be obtained when a dose of 2.5 or 5 g base/adult is given for 2–7 days [51–53].



V (pyrvinium pamoate)



VI (dithiazanine iodide)