PROGRESS IN DRUG RESEARCH
FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG
PROGRÈS DES RECHERCHES PHARMACEUTIQUES
VOL. 16

Progress in Drug Research
Fortschritte der Arzneimittelforschung
Progrès des recherches pharmaceutiques
Vol. 16

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ERNST JUCKER, Basel

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W. LENK, W. A. ZYGMUNT and P. A. TAVORMINA,
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PREFACE

Thirteen years have elapsed since the appearance of the first volume and it is with great pleasure that the Editor is now able to present volume 16. During these thirteen years various fields of drug research have undergone important, partly revolutionary, changes. A number of these have already been dealt with, so that the series PROGRESS IN DRUG RESEARCH contains a comprehensive review of a substantial part of our current knowledge. The Editor is particularly grateful for the opportunity of transmitting to those connected with the development of drugs the extensive knowledge of the Authors, who, without exception, are themselves actively engaged in research.

Drug research is currently in a state of transformation: reconsideration in the light of the past and reorientation with a view to the future. To a large extent this is due to the tumultuous developments in the last 20 years, developments which are unparalleled in the history of medicine and the consequences of which cannot yet be completely evaluated. Unfortunately, however, the current situation is not devoid of its unpleasant and even tragic aspects, aspects which fall outside the research worker's sphere or influence. Those connected with drug research, be they in industry, in universities or in clinics, are aware of these problems, and, as a result of this awareness, are all the more in need of an aid which will assist them in ascertaining the current position and in fixing future goals. The Editor and the Authors hope that in this respect also PROGRESS IN DRUG RESEARCH will be useful to research workers and further the development of our science.

In addition to thanking the Authors and the Publishers, the Editor would like to express the hope that the international collaboration, which has hitherto succeeded to such an exceptional extent to the benefit of all, will continue so that the value of this series as a reference work will steadily increase. Judging from the manner in which the series has thus far been received and from the volumes currently in preparation, this hope appears to be justified.

DR. E. JUCKER
SANDOZ AG, BASEL

VORWORT

Seit dem Erscheinen des ersten Bandes sind dreizehn Jahre vergangen, und der Herausgeber freut sich, der Fachwelt hiermit den 16. Band übergeben zu können. In dieser Zeitspanne haben auf verschiedenen Gebieten der Arzneimittelforschung wichtige, zum Teil umwälzende Entwicklungen stattgefunden; einzelne davon wurden in dieser Reihe bereits behandelt, mit dem Resultat, daß die FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG in ihrer Gesamtheit einen nicht unwesentlichen Teil unseres heutigen Wissens in zusammenfassender Darstellung enthalten. Der Herausgeber schätzt sich glücklich und ist dankbar für die Möglichkeit, mit diesem Werk das umfassende Wissen der Autoren, die ausnahmslos mitten in der aktiven Forschung stehen, zahlreichen in der Arzneimittelforschung Tätigen vermitteln zu dürfen.

Unser Forschungsgebiet befindet sich zurzeit in einer Phase des Umbruchs, der Besinnung auf Vergangenes und der Umorientierung auf die Zukunft. Diese Situation ist zum Teil der äussere Ausdruck und das Resultat der stürmischen Entwicklung der letzten 20 Jahre, die in der Geschichte der Medizin ohne Parallele dasteht und deren Folgeerscheinungen noch gar nicht überblickt werden können. Zum Teil aber hängt die jetzige Lage mit unerfreulichen und auch tragischen Ereignissen zusammen, die ausserhalb der Einflußsphäre der Arzneimittelforscher liegen. Die an der Arzneimittelforschung Beteiligten, seien sie Mitarbeiter der Industrie oder Forscher an Universitäten und Kliniken, sind sich der Problematik dieser Situation bewußt. Um so mehr bedürfen sie alle eines Hilfsmittels, das ihnen bei der Standortbestimmung und zur Neuorientierung dienen kann. Der Herausgeber und die Autoren hoffen, daß die FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG auch in dieser Hinsicht dem aktiven Forscher nützen und die Weiterentwicklung unserer Wissenschaft fördern können.

Zum Schluß dieser Betrachtungen möchte der Herausgeber nicht nur in gewohnter Weise den Autoren und dem Verlag danken, sondern darüber hinaus auch die Hoffnung aussprechen, daß die auf internationaler Ebene bisher so ersprießlich verlaufene Zusammenarbeit aller Beteiligten auch in Zukunft erhalten bleibt, um das Werk immer mehr zu einer wertvollen, viel benutzten Institution werden zu lassen. Die bisherige Aufnahme in Fachkreisen und die vorbereiteten weiteren Bände lassen diese Hoffnung als berechtigt erscheinen.

DR. E. JUCKER
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PRÉFACE

L'éditeur a aujourd'hui le plaisir de remettre au public le volume 16 de l'ouvrage, treize ans après la parution du premier. Durant ce laps de temps, les recherches pharmaceutiques ont subi, dans différents secteurs, des développements considérables, voire même, en partie, révolutionnaires; d'aucuns ont été déjà traités dans la présente série, si bien que les PROGRES DES RECHERCHES PHARMACEUTIQUES, pris dans leur ensemble, contiennent une part importante de nos connaissances actuelles sous forme d'aperçus généraux. L'éditeur est heureux de pouvoir, par ce canal, faire bénéficier les nombreuses personnes occupées aux recherches pharmaceutiques de la vaste science des auteurs, tous engagés activement dans la recherche et auxquels il se sent profondément obligé.

Notre champ de travail se trouve en ce moment dans une phase de transformation, de réflexion sur le passé et d'orientation nouvelle pour l'avenir. Cette situation est, en partie, la manifestation et le résultat du développement impétueux des vingt dernières années, développement sans précédent dans l'histoire de la médecine et dont les conséquences ne peuvent encore être évaluées; mais elle provient aussi, pour une part, d'événements malheureux, tragiques même, qui échappent à la sphère d'action de la recherche pharmaceutique. Ceux qui y collaborent, que ce soit dans l'industrie ou dans les universités et les cliniques, sont pleinement conscients des problèmes que pose cette situation nouvelle. Ils ont d'autant plus besoin d'un instrument qui puisse les aider à déterminer leur position et à se fixer une orientation nouvelle. L'éditeur et les auteurs espèrent que les PROGRÉS DES RECHERCHES PHARMACEUTIQUES s'avéreront utiles aux chercheurs, à cet égard aussi, et contribueront au développement ultérieur de leur discipline.

Au terme de ces considérations, l'éditeur ne voudrait pas seulement remercier, comme d'habitude, les auteurs et la maison d'edition, mais il tient en outre à exprimer l'espoir que la collaboration de tous les participants, qui s'est réalisée jusqu'ici au plan international d'une façon si satisfaisante, se poursuivra à l'avenir, pour que l'ouvrage devienne toujours davantage un instrument précieux et d'emploi fréquent. L'accueil qui'l a reçu dans les milieux intéressés et les articles à paraître dans les volumes suivants, en préparation, permettent de penser que cet espoir sera justifié.

DR. E. JUCKER
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Recent Developments in the Chemotherapy of Schistosomiasis

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1. Introduction

Schistosomiasis is a disease as old as antiquity, and together with other systemic and intestinal infections plagued military and civilian populations long before cause and effect relationships were hypothesized and definitively proven. The Ebers papyrus describes urinary symptomatology consistent with schistosomiasis; characteristic schistosome ova were identified from the kidneys of Egyptians mummified more than 3,000 years ago [148]. During the French occupation of Egypt (1799–1801), large numbers of troops exhibited symptoms of the disease. It is believed that Napoleon suffered urinary attacks and dysentery as a result of exposure to the infection [6].

In 1851, Theodore Bilharz discovered several schistosome worms during an autopsy of an Egyptian peasant. Owing to the morphology and location of the worms in the mesenteric veins, he called the parasite *Distoma haematobium* [18]. The genus was subsequently renamed *Schistosoma* (split-body) by WEINLAND [177] in 1858. Clinical experiences with schistosomiasis in Africa then became widespread [157].

Lateral and terminal spined eggs were observed for many years and it was thought that both kinds of eggs were products of *S. haematobium*. After a publication by Castellani in which only lateral spined eggs were described and after MANSON in 1902 reported similar findings in the feces of a patient from the island of Antigua in the West Indies, it was recognized that more than one kind of schistosome was responsible for infection [102]. SAMBON in 1907 proposed the name *S. mansoni* for the new species in honour of Sir PATRICK MANSON [151]. The third major human schistosome, *S. japonicum*, was described in 1904 [81].

The complex life cycle of the schistosomes, which eluded investigators for more than fifty years since the discovery of the parasite by Bilharz, was finally elucidated for *S. japonicum* in mice by MIYAIRI and SUZUKI [113] in 1913 and later confirmed by LEIPER and ATKINSON [95] who reported the snail as an obligate intermediate host. It remained for LEIPER [94] to show conclusively that the African schistosomes also employed snails as intermediate hosts in their life histories. MIYAGAWA and TAKEMOTO, and FAUST, in collaboration with MELENEY, HOFFMAN and JONES, reported in detail on the mammalian phases of the life cycles of *S. japonicum* [54, 112] and *S. mansoni* [52, 53].

Space does not permit detailed elaboration of the complex life cycle of the schistosomes that infect man; full descriptions may be obtained elsewhere [52, 53, 54, 112, 183]. Depending upon the particular species the three human schistosomes live as adults in the venous blood vessels in the vicinity of the bladder and/or intestine and rectum. Often a male and female will be paired in which case the female is held in a ventral groove or gynocophoric canal of the male. Oviposition takes place directly into the smaller venules and the eggs work their way through the wall of the blood vessel and eventually reach the lumen of the intestine or bladder and are voided with the feces and/or urine. Many of the eggs are filtered out in the tissues of the bowel and bladder and

are unable to complete the life cycle. Large numbers of eggs, especially in the case of infection with *S. japonicum*, are swept into the liver via the portal circulation where they become walled off, encapsulated, and cannot continue further development thus contributing to the pathogenesis of the disease. The viable egg passed with the feces or urine must be deposited in fresh water in order to hatch and release a miracidium. Since this larval form has a relatively short, free running life span, it must penetrate the soft tissues of a suitable snail host in which a series of intramolluscal reproductive developments take place. Under optimum conditions, fork-tailed cercariae, the infective forms, break out of the snail within 4–6 weeks after invasion by the miracidium; infected snails may produce hundreds of cercariae daily for several months. The molluscan intermediate hosts for *S. mansoni*, *S. haematobium* and *S. japonicum* are members of the genera *Biomphalaria* (also referred to as *Australorbis* and *Tropicorbis*), *Bulinus* and *Oncomelania*, respectively. Man becomes infected by the penetration of an actively swimming cercariae. The invasive larva, which superficially resembles the adult form, loses its tail and gains access to the circulatory system where it undergoes a series of differential transformations in the pulmonary and intrahepatic portal veins before becoming a sexually mature parasite. The prepatent period for *S. japonicum* is 5 or 6 weeks, for *S. mansoni* 7 or 8 weeks and for *S. haematobium* 10–12 weeks.

In man the adult worms of *S. mansoni* are found in the hemorrhoidal venous plexus; those of *S. haematobium* primarily inhabit the vessels of the vesicular and pelvic plexus of the venous circulation in the vicinity of the urinary bladder and those of *S. japonicum* are found in the radicles of the superior mesenteric veins draining the small intestine. The trematodes range in size from 7 to 20 mm with the females reaching the upper limit. The latter deposit eggs for many years.

Human pollution constitutes the principal method of perpetuating infections with the schistosomes. Although wild rodents and nonhuman primates have been experimentally infected [63, 79, 88, 89, 104] or found to be naturally infected [104, 122, 123, 167] they do not constitute a significant reservoir for the maintenance of the adult stage of *S. mansoni* or *S. haematobium*. Nonhuman mammalian hosts, however, are important reservoirs for *S. japonicum* and, therefore, contribute to a zoonatic problem whose magnitude depends on the strain and geographical location of the parasite [121].

The prevalence of schistosomiasis is widespread [109, 182]. A conservative estimate of the world's population exposed to infection has been given at 354 million with 118 million cases [184]. The seriousness of the infection and its impact on the economy and development of communities in areas of transmission is striking [33, 48, 110, 184]. Literally hundreds of millions of dollars are lost annually in reduced labor output and decreased productivity, incurrence of medical expenses, costs of public health measures and rehabilitation programs. The disabling effects of schistosomiasis, especially in the adolescent and the young working population, is incalculable in terms of dollar estimates.