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The Chemotherapy of Amoebiasis

By G. Woolfe

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原书缺页

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VORWORT

Die Arzneimittelforschung hat sich in den letzten zwanzig Jahren stürmisch entwickelt und bewegt sich nicht mehr nur auf den naheliegenden Disziplinen der Chemie, Pharmakologie, Toxikologie und Medizin, sondern greift auch auf die der Physiologie, Biochemie, physikalischen Chemie und Physik über. Dem einzelnen ist es deshalb kaum noch möglich, die Originalliteratur zu verfolgen, soweit sie außerhalb seiner eigenen Forschungsrichtung liegt, und auch da besteht die große Gefahr der allzu engen Spezialisierung. Die Erkenntnis dieser Entwicklung und ihrer Folgeerscheinungen hat den Herausgeber vor einigen Jahren dazu bewogen, diese Monographienreihe ins Leben zu rufen, und er empfindet große Genugtuung, hiermit bereits den achten Band seinen Lesern übergeben zu können. Er ergreift freudig die Gelegenheit, nicht nur den Autoren für ihre Bereitwilligkeit, mit welcher sie einzelne Forschungsgebiete in Übersichtsreferaten dargestellt haben, sondern auch befreundeten Forschern und Fachkollegen für ihre vielen wertvollen Anregungen, Kritiken und Vorschläge zu danken, ist es ihm doch nur dank dieser Unterstützung von seiten der Fachwelt ermöglicht worden, diese Zusammenarbeit auf internationaler Ebene zu organisieren und die *Fortschritte der Arzneimittelforschung* zu einem nützlichen Werk auszugestalten. Er hofft, daß ihm diese wertvolle Unterstützung, ohne die die Fortsetzung eines derartigen Werkes unmöglich wäre, auch weiterhin in vollem Umfang erhalten bleibt.

In den bis jetzt vorliegenden acht Bänden wurden ganz verschiedene Gebiete der Arzneimittelforschung dargestellt, und die Arbeiten für die Berichterstattung werden nach verschiedenen aktuellen Richtungen hin weiter vorgetrieben. So nehmen die *Fortschritte* in ihrer Gesamtheit immer mehr den Charakter eines Nachschlagewerkes an, das aber den Vorteil hat, sich stets zu erneuern und aktuell zu bleiben. Obwohl die vornehmste Aufgabe einer solchen Monographienreihe darin zu erblicken ist, daß sie über die neusten Ergebnisse auf verschiedenen Gebieten rasch und gründlich Auskunft gibt, zeichnet sich darüber hinaus noch eine weitere Möglichkeit immer deutlicher ab: Die einzelnen Beiträge liefern dem interessierten Forscher eine synoptische Darstellung der verschiedenen behandelten Gebiete, woraus er Zusammenhänge zwischen den verschiedenen Disziplinen und Beziehungen zwischen den einzelnen Faktoren, die für das Zustandekommen der Arzneimittelwirkungen überhaupt verantwortlich sind, herleiten kann, was seinen eigenen Forschungen neue Impulse verleihen und Anregungen für neue Forschungsrichtungen bieten wird. Sollte diese erweiterte Funktion den *Fortschritten* ermöglichen, einen direkten Beitrag an den Fortschritt der Therapie zu leisten, dann bedeutet dies die Erreichung eines Zieles, das sich der Herausgeber gesteckt hat.

Der Herausgeber möchte mit der Übergabe dieses Bandes seiner Dankbarkeit den Autoren gegenüber Ausdruck geben. Der Verlag und die Druckerei Birkhäuser AG, Basel, haben diesem Werk seit seinem Bestehen alle Unterstützung angedeihen lassen, was in der raschen Drucklegung und der sorgfältigen und sachdienlichen Ausstattung sichtbar ist; auch dafür sei bestens gedankt.

PREFACE

Drug research has developed exceedingly rapidly in the last twenty years and today includes not only such allied subjects as chemistry, pharmacology, toxicology, and medicine, but also physiology, biochemistry, physical chemistry, and physics. For this reason, individuals can hardly hope to follow research in fields other than their own, and even then there is danger of over-specialization. This development and its constricting consequences made the editor a few years ago initiate this series of monographs and he has pleasure in presenting an eighth volume. Thanks both to the willingness of outstanding specialists to deal with individual topics in comprehensive articles and to the many suggestions, proposals and criticisms from his colleagues, the editor has been able to organize cooperation on an international level and to make *Progress in Drug Research* really useful. The editor hopes that also in the future he may rely on the help so willingly extended to him by experts without whose assistance such a work would be impossible.

Various aspects of drug research have been treated in the first eight volumes and other subjects are in preparation. *Progress in Drug Research* is now increasingly assuming the character of a work of reference, albeit one which has the advantage of perpetual youth and actuality. Although the principal function of this series of monographs consists in making available information about various topics quickly and exhaustively, a further characteristic is becoming apparent. The drug researcher can perceive from a study of the different articles a context between various subjects and relations between factors which are responsible for engendering a pharmaceutical effect. In this way he is given a new stimulus in relation to both the field and the direction of his own research work. This wider function of *Progress in Drug Research* should result in direct contributions to further progress in therapy.

The editor would like to extend his thanks to the authors on the occasion of the publication of this volume. The publishers and printers, Birkhäuser AG, Basel, have also given every assistance in the production of this work since its inception, as is apparent from the rapid printing and expert presentation. The editor's thanks are also due for their valuable collaboration.

PRÉFACE

Durant les vingt dernières années, la recherche pharmaceutique a pris un cours impétueux et elle embrasse aujourd'hui non plus seulement les disciplines immédiatement voisines: chimie, pharmacologie, toxicologie et médecine, mais encore la physiologie, la biochimie, la chimie physique et la physique. Aussi n'est-il plus guère possible au chercheur isolé de se maintenir au courant de domaines autres que les siens propres et il se trouve exposé dès lors au danger d'une étroite spécialisation. D'avoir vu ce développement et d'en avoir entrevu les conséquences, l'éditeur s'est senti mû, il y a quelques années, à créer la présente série de monographies; il a maintenant le plaisir d'en remettre aux lecteurs le huitième volume. L'obligeance de collègues éminents qui se sont montrés prêts à donner de leurs travaux des aperçus d'ensemble, mais aussi les nombreuses suggestions, propositions et critiques émises par des chercheurs amis ont permis à l'éditeur d'organiser cette collaboration sur un plan international et de faire des *Progrès des recherches pharmaceutiques* un organe utile. Il espère donc que les milieux scientifiques compétents, sans l'aide desquels un tel ouvrage serait impossible, lui accorderont à l'avenir le même appui large et obligeant que jusqu'ici.

Dans les huit volumes déjà parus sont traités divers domaines de la chimie pharmaceutique, tandis que des exposés sur d'autres directions actuelles de la recherche sont en préparation. Ainsi, les *Progrès*, considérés dans leur ensemble, prennent toujours plus le caractère d'un ouvrage de référence, avec l'avantage, toutefois, de pouvoir se renouveler constamment et de rester d'actualité. Le premier but d'une série de monographies de ce genre est sans doute d'apporter une information rapide et approfondie sur divers domaines. Cependant, une seconde possibilité se dessine de plus en plus nettement: en effet, un lecteur engagé dans la recherche peut, à partir des différents articles, établir des relations entre les diverses disciplines ou entre les facteurs qui déterminent les effets thérapeutiques et, par là, donner des impulsions nouvelles à ses recherches ou découvrir l'idée d'une direction de travail nouvelle. Cette fonction élargie des *Progrès* devrait constituer une contribution directe à l'avancement de la thérapeutique.

En remettant ce volume au public, l'éditeur tient à exprimer sa vive reconnaissance aux auteurs. Les Editions et l'Imprimerie Birkhäuser S.A., Bâle, ont voué tous leurs soins à cet ouvrage dès les débuts, ce qui se manifeste par une impression rapide et une présentation soignée et adéquate; à elles aussi s'adressent ses remerciements sincères.

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The Chemotherapy of Amoebiasis

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1. Introduction

Some twelve years ago D'ANTONI [1] at the end of a paper on 'Concepts and misconceptions in amebiasis' summarized the position as follows: 'Amebiasis at the present time is a confused, incompletely understood, and much misunderstood, disease. The real prevalence is unknown. The epidemiology remains to be clarified. The clinical manifestations are typically atypical, and are frequently not referable to the intestinal tract. The diagnosis of the disease, even though it is entirely a laboratory matter is sometimes in dispute. The criteria of cure differ from physician to physician, and no entirely satisfactory amebicidal drug is presently available...' In the intervening years several hundred papers dealing with the various aspects of amoebiasis have been published, but though we now have better drugs available, the situation otherwise is little changed. There is still argument about the pathology of the infection, about the epidemiology of amoebiasis, about the need to treat those carrying *Entamoeba histolytica* in their intestines but free from symptoms of infection, etc. Whilst BOYD [2, 3] queries the need to treat cyst-passers, even those who handle food, other authorities (e.g. MANSON BAHR [4], MCROBERT [5], STAMM [6]) believe that 'carrier cases' should be treated both to prevent more serious developments in the individual and to prevent the spread of infection. There does, however, seem little doubt that *Entamoeba histolytica* is, at least potentially, pathogenic whereas other species of *Entamoeba*, or different genera of amoebae, are of much less importance medically. It is intended, therefore, in dealing with the chemotherapy of amoebiasis here to concentrate entirely on *E. histolytica* and to ignore all other amoebae. Several text books deal in great detail with the clinical aspects of amoebiasis, e.g. FAUST [7] and REES [8]; the most recent (WILMOT [9]) presents an excellent picture of amoebiasis from the clinician's point of view, and mentions many recent developments in the broad field of amoebiasis.

Methods which have been used to test amoebicides in the laboratory, both *in vitro* and in experimental animals have been reviewed recently (WOOLFE [10]) and it is not intended to deal with the very large numbers of techniques which have been described, other than to mention the most important recent developments. Nor, in view of the review mentioned and those of ELSLAGER [11] and DRUEY [12], is it intended to survey the broad field of substances which have been tested as amoebicides. Only those drugs which are being used clinically and on which considerable work is still going on will be mentioned; this means, of course, that many lines of approach which at the moment show promise, but nothing more, will be omitted.

2. Techniques

2.1 *In vitro*

As has been shown repeatedly, results of *in vitro* tests for amoebicidal activity may be very misleading. It is highly desirable that any *in vitro* test used should be comparative, i.e. standard amoebicides should be tested side by side

with new compounds, should use standard monophasic media, should use strains of amoeba with consistent associate or associates, and should distinguish between direct effect on the amoeba and effect mediated *via* effect on culture associates. Most tests employed now fulfil these criteria.

2.2 *In vivo*

For tests for activity against intestinal infections the newly weaned rat is used almost universally. The use of other host species is relatively rare, though a recent note on the use of hamsters for drug tests may revive interest in this species (SAXE and BLANKENSHIP [13]). The kitten and the dog have now been almost entirely abandoned as experimental hosts for amoebae—kittens because the infection produced is fulminating and cannot be controlled by the use of drugs which are active clinically, dogs because the fish diet often used to 'promote' the amoebic infection will, of itself, produce colitis (ARTIGAS and BEAVER [14], VILLAREJOS [15]).

For tests of drugs against amoebic hepatitis, liver abscess in the hamster is used almost universally, as other animals are thought to be less susceptible (REINERSTON and THOMPSON [16], WILLIAMS [17], GHIONE [18]). However, TANCOCK (paper in press) has recently reinvestigated the use of mice, and has found that with repeated liver passage of *E. histolytica* in mice, virulence is enhanced sufficiently to permit reasonable uniformity of infection, and she suggests that use of the liver abscess in mice may prove suitable for examining new compounds for potentially useful activity.

3. Drugs for the Treatment of Amoebiasis

As was mentioned in the Introduction, only those drugs which have achieved clinical use are to be discussed, together with an account of recent work on them and on their analogues. Many interesting series must, therefore, be omitted because they have not reached the stage of clinical use, though a number are under trial.

3.1 *Emetine and its Derivatives*

Although emetine was first described by PELLETIER in 1817 and ipecacuanha had long been used in the treatment of dysenteries, it was not until 1912 that VEDDER [19] demonstrated the activity of emetine hydrochloride against amoebae *in vitro*, and ROGERS [20], after showing that emetine could destroy *E. histolytica* in mucus containing large numbers of amoebae, demonstrated the value of the alkaloid given parenterally to patients suffering from acute amoebic dysentery or hepatitis. Emetine was quickly taken into use, but the extent of its use has fluctuated because of the relatively narrow margin between effec-