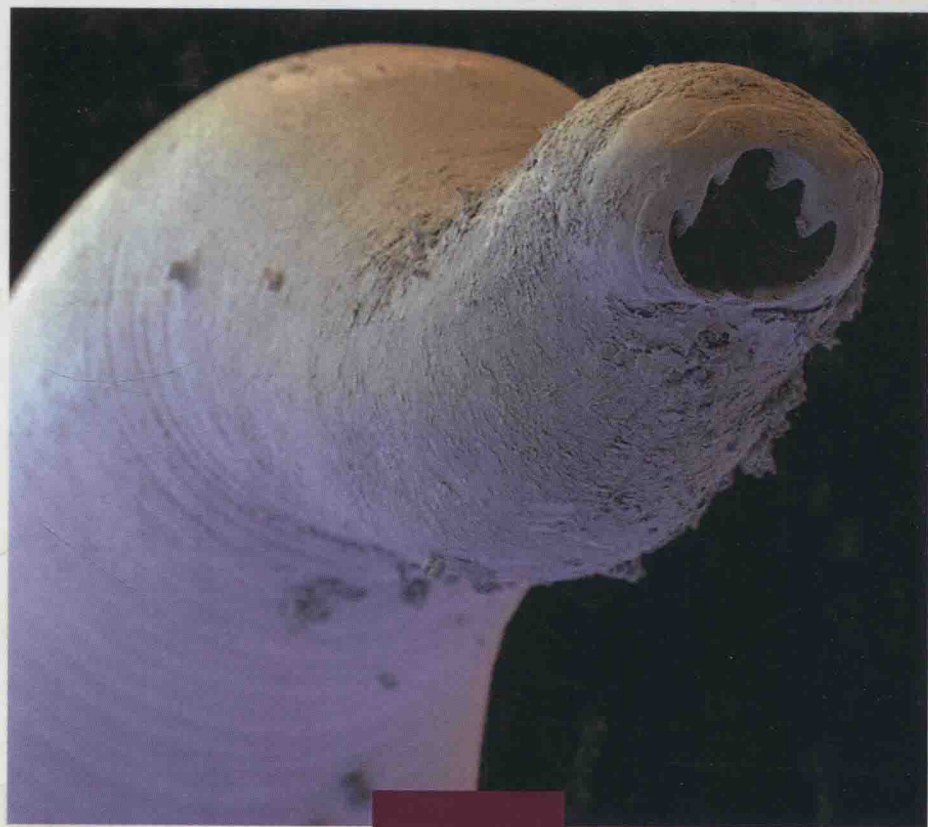


# ADVANCES IN PARASITOLOGY



58

Edited by

J.R. BAKER R. MULLER D. ROLLINSON

# *Advances in* PARASITOLOGY

*Edited by*

J.R. BAKER

*Royal Society of Tropical Medicine and Hygiene,  
London, England*

R. MULLER

*London School of Hygiene and Tropical Medicine,  
London, England*

and

D. ROLLINSON

*The Natural History Museum,  
London, England*

VOLUME 58



ELSEVIER  
ACADEMIC  
PRESS

Amsterdam Boston Heidelberg London New York Oxford Paris  
San Diego San Francisco Singapore Sydney Tokyo

ELSEVIER B.V. Sara Burgerhartstraat 25 P.O. Box 211, 1000 AE Amsterdam, The Netherlands	ELSEVIER Inc. 525 B Street Suite 1900, San Diego CA 92101-4495, USA	ELSEVIER Ltd The Boulevard Langford Lane, Kidlington Oxford OX5 1GB, UK	ELSEVIER Ltd 84 Theobalds Road London WC1X 8RR UK
--	--	--	--

© 2004 Elsevier Ltd. All rights reserved.

This work is protected under copyright by Elsevier Ltd, and the following terms and conditions apply to its use:

#### **Photocopying**

Single photocopies of single chapters may be made for personal use as allowed by national copyright laws. Permission of the Publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

Permissions may be sought directly from Elsevier's Rights Department in Oxford, UK: phone (+44) 1865 843830, fax (+44) 1865 853333, e-mail: [permissions@elsevier.com](mailto:permissions@elsevier.com). Requests may also be completed on-line via the Elsevier homepage (<http://www.elsevier.com/locate/permissions>).

In the USA, users may clear permissions and make payments through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA; phone: (+1) (978) 7508400, fax: (+1) (978) 7504744, and in the UK through the Copyright Licensing Agency Rapid Clearance Service (CLARCS), 90 Tottenham Court Road, London W1P 0LP, UK; phone: (+44) 20 7631 5555; fax: (+44) 20 7631 5500. Other countries may have a local reprographic rights agency for payments.

#### **Derivative Works**

Tables of contents may be reproduced for internal circulation, but permission of the Publisher is required for external resale or distribution of such material. Permission of the Publisher is required for all other derivative works, including compilations and translations.

#### **Electronic Storage or Usage**

Permission of the Publisher is required to store or use electronically any material contained in this work, including any chapter or part of a chapter.

Except as outlined above, no part of this work may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the Publisher.

Address permissions requests to: Elsevier's Rights Department, at the fax and e-mail addresses noted above.

#### **Notice**

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

First edition 2004

British Library Cataloguing in Publication Data  
A catalogue record is available from the British Library.

ISBN: 0-12-031758-3  
ISSN: 0065-308X

∞ The paper used in this publication meets the requirements of ANSI/NISO Z39.48-1992 (Permanence of Paper).

Transferred to digital print 2007

Printed and bound by CPI Antony Rowe, Eastbourne

*Advances in*  
PARASITOLOGY

VOLUME 58

## Editorial Board

- M. Coluzzi**, Director, Istituto de Parassitologia, Università Degli Studi di Roma 'La Sapienza', P. le A. Moro 5, 00185 Roma, Italy
- C. Combes**, Laboratoire de Biologie Animale, Université de Perpignan, Centre de Biologie et d'Ecologie Tropicale et Méditerranéenne, Avenue de Villeneuve, 66860 Perpignan Cedex, France
- D.D. Despommier**, Division of Tropical Medicine and Environmental Sciences, Department of Microbiology, Columbia University, 630 West 168th Street, New York, NY 10032, USA
- J.J. Shaw**, Instituto de Ciências Biomédicas, Universidade de São Paulo, av. Prof. Lineu Prestes 1374, 05508-900, Cidade Universitária, São Paulo, SP, Brazil
- K. Tanabe**, Laboratory of Biology, Osaka Institute of Technology, 5-16-1 Ohmiya Asahi-Ku, Osaka, 535, Japan
- P. Wenk**, Falkenweg 69, D-72076 Tübingen, Germany

## CONTRIBUTORS TO VOLUME 58

- J.-C. ANTOINE, *Unité d'Immunophysiologie et Parasitisme Intracellulaire, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex 15, France*
- J. BETHONY, *Cellular and Molecular Immunology Laboratory, "René Rachou" Research Centre FIOCRUZ, Barro Preto – CEP 30190-002, Belo Horizonte, Brazil*
- S. BROOKER, *Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK*
- N. COURRET, *Unité d'Immunophysiologie et Parasitisme Intracellulaire, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex 15, France*
- A. J. DAVIES, *School of Life Sciences, Kingston University, Penrhyn Road, Kingston upon Thames, Surrey, KT1 2EE, UK*
- B. FRIED, *Department of Biology, Lafayette College, Easton, Pennsylvania 18042, USA*
- T. K. GRACZYK, *The W. Harry Feinstone Department of Molecular Microbiology and Immunology, and Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, 615 N. Wolfe Street, Baltimore, Maryland 21205, USA*
- P. J. HOTEZ, *Department of Microbiology and Tropical Medicine, The George Washington University, Washington DC 20037, USA*
- T. LANG, *Unité d'Immunophysiologie et Parasitisme Intracellulaire, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex 15, France*
- P. T. MONIS, *Australian Water Quality Centre, South Australian Water Corporation and Cooperative Research Centre for Water Quality and Treatment, Private Mail Bag 3, Salisbury, SA 5108, Australia*

E. PRINA, *Unité d'Immunophysiologie et Parasitisme Intracellulaire, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex 15, France*

N. J. SMIT, *Department of Zoology, Rand Afrikaans University, P.O. Box 524, Auckland Park 2006, South Africa*

R. C. A. THOMPSON, *WHO Collaborating Centre for the Molecular Epidemiology of Parasitic Infections, Veterinary and Biomedical Sciences, Murdoch University, Murdoch, WA 6150, Australia*

## PREFACE

The opening paper in this volume concerns the intricate interactions between *Leishmania* and antigen-presenting cells of the mammalian host. Jean-Claude Antoine, Eric Prina, Nathalie Courret and Thierry Lang from the Institut Pasteur, Paris provide a detailed overview of how *Leishmania* spp. interact with two cell types, macrophages and dendritic cells, and describe some of the strategies used by *Leishmania* spp. to survive in these inducible or antigen-presenting cells. This is a fascinating account of the complex interactions that can occur between host and parasites. The authors highlight a number of questions and challenges in need of further research.

In the next paper, Andrew Thompson of the University of Melbourne, Australia and Paul T. Monis from the Australian Water Quality Centre, Salisbury consider the variation observed in *Giardia* and the implications for taxonomy and epidemiology. *Giardia* is an intestinal parasite often encountered in humans, which can cause acute or chronic diarrhoea, dehydration, abdominal pain, nausea, vomiting and weight loss. Awareness of the parasite goes back a long time; indeed *Giardia* might have been observed as far back as 1681 by Antonie van Leeuwenhoek. It is interesting to read how the story has unfolded over the years and to appreciate the considerable ongoing debate that has concerned *Giardia* especially relating to the taxonomy, phylogeny and host specificity. The application of new molecular tools for identification and diagnosis are helping to unravel the mysteries of the transmission and host specificity of this parasite. Undoubtedly the findings have relevance to the control of giardiasis. The authors propose that this new information be reflected in the redesignation of several species of *Giardia* described previously.



Bernard Fried at Lafayette College, Pennsylvania and Thaddeus Graczyk of Johns Hopkins University, both in the USA, continue the series of reviews on echinostomes (previous reviews in volumes 29, 38 and 49 of *Advances in Parasitology*). The 10 species of *Echinostoma* considered in the present review do not include the most important medical or veterinary parasites, although they can play a significant role in causing disease in waterfowl and aquatic mammals. Some species are also widely used as experimental models since the complete life cycles can be conveniently maintained in the laboratory. This has enabled them to be used to help elucidate many aspects of trematode biology including physiological, biochemical, immunological and molecular studies. These aspects, as well as systematic and descriptive studies, are comprehensively reviewed.

Human hookworm infection is extremely common with estimates of over 700 million cases in the tropics and subtropics. Often occurring together with other intestinal helminths, hookworm infection remains an important public health problem. Indeed there has been a gradual realization that the effects of infection are greater than had been assumed in the past. In this review, Simon Brooker from the London School of Hygiene and Tropical Medicine, UK, Jeffrey Bethony from the "René Rachou" Research Centre FIOCRUZ, Brazil and Peter Hotez from The George Washington University, USA provide an extensive overview of current knowledge highlighting recent advances in our understanding of the biology, immunology, epidemiology and public health significance of hookworm infections. It is extremely encouraging that large-scale treatment campaigns are under way around the world and the authors consider the advantages of regular population-based chemotherapy.

Nico Smit, of Rand Afrikaans University in South Africa, and Angela Davies, of Kingston University in the UK, complete the volume with an account of the relatively little-known but fascinating gnathiid isopods. These small crustacea have free-living, non-feeding adults and parasitic juveniles, comprising several larval stages, which feed on the blood and tissue fluids of fishes. Apart from the sometimes considerable pathogenic effects to the fish of this parasitism, at least one genus of gnathiid (*Gnathia*) serves as a vector

of the apicomplexan protozoan *Haemogregarina bigemina*, a widespread parasite of teleosts. Smit and Davies suggest that further investigation of the capacity of gnathiids to act as vectors of other parasitic groups is warranted.

John Baker  
Ralph Muller  
David Rollinson

# CONTENTS

CONTRIBUTORS TO VOLUME 58 .....	v
PREFACE .....	vii

## ***Leishmania* spp.: on the Interactions They Establish with Antigen-Presenting Cells of their Mammalian Hosts**

Jean-Claude Antoine, Eric Prina, Nathalie Courret and Thierry Lang

Abstract .....	2
1. Introductory Remarks .....	3
2. The MΦs as Host Cells for <i>Leishmania</i> spp. ....	17
3. The MΦs as Cells Presenting <i>Leishmania</i> Antigens .....	24
4. Ability of Infected MΦs to Destroy <i>Leishmania</i> Parasites They Harbour .....	32
5. The DCs as Cells That Can Also Shelter <i>Leishmania</i> spp. ....	37
6. Role of DCs in the Presentation of <i>Leishmania</i> Antigens to Naive and Activated Specific T Lymphocytes .....	41
7. The Potential of Infected APCs or APCs Loaded with <i>Leishmania</i> Antigens as Vaccines or Therapeutic Agents .....	50
8. Conclusions .....	53
Acknowledgements .....	55
References .....	56

## **Variation in *Giardia*: Implications for Taxonomy and Epidemiology**

R.C.A. Thompson and P.T. Monis

Abstract .....	70
1. Introduction .....	70
2. Current Taxonomy and Nomenclature .....	75

3. Phenotypic Evidence for Variation in <i>G. duodenalis</i> .....	85
4. Genetic Characterization of <i>Giardia</i> and Prospects for a Revised Taxonomy .....	88
5. Epidemiology and Transmission .....	105
6. Perspectives for the Future .....	119
References .....	121

## Recent Advances in the Biology of *Echinostoma* species in the "revolutum" Group

Bernard Fried and Thaddeus K. Graczyk

Abstract .....	140
1. Introduction .....	140
2. <i>Echinostoma caproni</i> .....	142
3. <i>Echinostoma trivolvis</i> .....	152
4. <i>Echinostoma paraensei</i> .....	165
5. <i>Echinostoma revolutum</i> .....	169
6. <i>Echinostoma friedi</i> .....	174
7. <i>Echinostoma miyagawai</i> .....	175
8. <i>Echinostoma echinatum</i> .....	176
9. <i>Echinostoma parvocirrus</i> .....	177
10. <i>Echinostoma luisreyi</i> .....	177
11. <i>Echinostoma jurini</i> .....	178
12. Concluding Remarks .....	178
Acknowledgements .....	179
References .....	180

## Human Hookworm Infection in the 21st Century

Simon Brooker, Jeffrey Bethony and Peter J. Hotez

Abstract .....	198
1. Introduction .....	199
2. Biology .....	201
3. Immune Responses to Hookworm .....	211
4. Epidemiology and Transmission Dynamics .....	220
5. Public Health Consequences .....	233
6. Global Distribution and Disease Burden .....	242
7. Strategies for Control .....	250

8. Future Directions .....	261
Acknowledgements .....	262
References .....	263

## **The Curious Life-Style of the Parasitic Stages of Gnathiid Isopods**

N.J. Smit and A.J. Davies

Abstract .....	289
1. Introduction .....	290
2. Gnathiid Phylogeny, Taxonomy and Morphology .....	303
3. Life Cycles of Gnathiids .....	317
4. Adaptation of Juveniles to Blood Feeding .....	334
5. Pathology and Transmission of Infection Associated with Blood Feeding .....	358
6. Behaviour of Gnathiid Juveniles and the Role of Cleaner Fishes in their Removal from Clients .....	369
7. Conclusion .....	373
Acknowledgements .....	377
References .....	378
INDEX .....	393
CONTENTS OF VOLUMES IN THIS SERIES .....	405

The colour plate section appears between pages 50 and 51.

# ***Leishmania* spp.: on the Interactions They Establish with Antigen-Presenting Cells of their Mammalian Hosts**

Jean-Claude Antoine\*, Eric Prina, Nathalie Courret and  
Thierry Lang

*Unité d'Immunophysiologie et Parasitisme Intracellulaire, Institut Pasteur,  
25 rue du Dr Roux, 75724 Paris cedex 15, France*

Abstract . . . . .	2
1. Introductory Remarks . . . . .	3
1.1. The Life Cycles of <i>Leishmania</i> spp. . . . .	3
1.2. "Classical and Natural Experimental Models" of Leishmaniases . . . . .	6
1.3. Cells Containing <i>Leishmania</i> or <i>Leishmania</i> Antigens in Infected Mice . . . . .	8
1.4. Background on MΦs and DCs: The Sentinels of the Body . .	10
1.5. Background on the Biosynthesis of MHC Class I and II Molecules by APCs and Formation of Peptide-MHC Molecule Complexes . . . . .	14
2. The MΦs as Host Cells for <i>Leishmania</i> spp. . . . .	17
2.1. Binding and Internalization of Promastigotes and Amastigotes. . . . .	17
2.2. The Formation of PVs After Promastigote or Amastigote Phagocytosis and the Adaptation of Parasites to These Intracellular Niches . . . . .	19
3. The MΦs as Cells Presenting <i>Leishmania</i> Antigens . . . . .	24
3.1. PVs and the Ag Presentation Machinery. . . . .	24
3.2. MHC I Ag Presentation by Infected MΦs . . . . .	25
3.3. MHC II Ag Presentation by Infected MΦs. . . . .	26
3.4. Expression of Co-stimulatory Molecules by Infected MΦs . .	29
3.5. <i>In vivo</i> Data . . . . .	31

\*Author for correspondence. E-mail: jantoine@pasteur.fr

4. Ability of Infected MΦs to Destroy <i>Leishmania</i> Parasites They Harbour . . . . .	32
4.1. The Different Pathways Leading to the Development of Leishmanicidal Properties . . . . .	32
4.2. Mechanisms of <i>Leishmania</i> Killing . . . . .	35
4.3. How <i>Leishmania</i> Evade the Killing Mechanisms? . . . . .	36
4.4. In Susceptible Mice, MΦs Can Follow an Alternative Activation Pathway Leading to Uncontrolled Parasite Growth . . . . .	37
5. The DCs as Cells That Can Also Shelter <i>Leishmania</i> spp. . . . .	37
5.1. Binding and Phagocytosis of Promastigotes and Amastigotes. . . . .	37
5.2. Phagosomal Compartments Housing Parasites in DCs. . . . .	40
6. Role of DCs in the Presentation of <i>Leishmania</i> Antigens to Naive and Activated Specific T Lymphocytes . . . . .	41
6.1. Ability of <i>Leishmania</i> spp. to Induce DC Maturation and Migration . . . . .	41
6.2. MHC I and MHC II Ag Presentation by DCs Put in Contact with Parasites or <i>Leishmania</i> Ags. . . . .	43
6.3. Possible Mechanisms used by <i>Leishmania</i> spp. to Limit Ag Presentation by DCs . . . . .	48
6.4. DCs and the Polarization of <i>Leishmania</i> -Specific CD4 T Lymphocytes. . . . .	49
7. The Potential of Infected APCs or APCs Loaded with <i>Leishmania</i> Antigens as Vaccines or Therapeutic Agents . . . . .	50
7.1. APCs as Vaccines . . . . .	50
7.2. APCs as Therapeutic Agents. . . . .	53
8. Conclusions . . . . .	53
Acknowledgements . . . . .	55
References . . . . .	56

## ABSTRACT

Identification of macrophages as host cells for the mammalian stage of *Leishmania* spp. traces back to about 40 years ago, but many questions concerning the ways these parasites establish themselves in these cells, which are endowed with potent innate microbicidal mechanisms, are still unanswered. It is known that microbicidal activities of macrophages can be enhanced or induced by effector T lymphocytes following the presentation of antigens via MHC class I or class II molecules expressed at the macrophage plasma membrane. However,

*Leishmania* spp. have evolved mechanisms to evade or to interfere with antigen presentation processes, allowing parasites to partially resist these T cell-mediated immune responses. Recently, the presence of *Leishmania* amastigotes within dendritic cells has been reported suggesting that they could also be host cells for these parasites. Dendritic cells have been described as the only cells able to induce the activation of naive T lymphocytes. However, certain *Leishmania* species infect dendritic cells without inducing their maturation and impair the migration of these cells, which could delay the onset of the adaptive immune responses as both processes are required for naive T cell activation. This review examines how *Leishmania* spp. interact with these two cell types, macrophages and dendritic cells, and describes some of the strategies used by *Leishmania* spp. to survive in these inducible or constitutive antigen-presenting cells.

## 1. INTRODUCTORY REMARKS

### 1.1. The Life Cycles of *Leishmania* spp.

*Leishmania* spp. are heteroxenous, digenetic protozoan parasites and as such they live successively in two hosts, namely hematophagous insect vectors known as sand flies and some mammals playing the role of reservoirs, from which these infectious agents can be transmitted to other organisms of the same species or of a different species, including humans (for a review see Peters and Killick-Kendrick, 1987a; Schnur and Greenblatt, 1995). In female sand flies, *Leishmania* spp. exist extracellularly in the lumen of the digestive tract where they adopt a flagellated, elongated promastigote form and go through several differentiation stages. After a differentiation process called metacyclogenesis, promastigotes infective for mammals, termed metacyclic promastigotes, accumulate in the anterior parts of the digestive tract, from where they can be inoculated into the dermis of mammals during a blood meal (Rogers *et al.*, 2002). In mammals, *Leishmania* spp. are obligate intracellular parasites. Indeed, after the bite of an infected sand fly, at least some of the injected metacyclics are rapidly engulfed



by resident dermal phagocytic cells or cells rapidly recruited from the epidermis or the blood. During the early stages of the infection, a large part of the cells internalizing parasites appears to be macrophages (MΦs), inside which promastigotes differentiate into egg-shaped amastigotes devoid of the external flagellum. This process takes several days and occurs within organelles named parasitophorous vacuoles (PVs), the morphology of which, and at least certain properties vary with different *Leishmania* species (Antoine *et al.*, 1998; Courret *et al.*, 2001). The life cycle is completed when a sand fly takes a blood meal on a parasitized mammal. During this process, the vector can be infected by free amastigotes or by infected mammalian cells located in the skin dermis. In the gut of the insect, the amastigotes differentiate rapidly into promastigotes. As an example, the cycle of *L. amazonensis* is presented in Figure 1.

Humans can also be infected by numerous *Leishmania* species, but for most of them they are accidental hosts. About 12 million people distributed in 88 countries are suffering from leishmaniasis in the world, and it is estimated that 2 million new cases arise each year. In Europe, Africa and Asia, *L. donovani*, *L. infantum*, *L. major*, *L. tropica* and *L. aethiopica* are the main species infecting humans, whereas in South and Central America mainly *L. chagasi*, *L. mexicana*, *L. amazonensis*, *L. guyanensis* and *L. braziliensis* are responsible for leishmaniases. According to the *Leishmania* species initiating infection and their genetic/immunologic status, humans can remain asymptomatic or display more or less severe pathologic processes. Four major forms of human leishmaniases have been described: cutaneous, diffuse cutaneous, mucocutaneous and visceral. Cutaneous leishmaniases are generally benign. Parasites develop locally in the skin at the sites where infected sand flies have inoculated metacyclic promastigotes. In contrast, visceral leishmaniases are fatal in the absence of treatment. In these forms, parasites develop mainly in the liver, the spleen and bone marrow (for a review see Peters and Killick-Kendrick, 1987b; Schnur and Greenblatt, 1995).

As to the wild mammalian reservoirs, which in many *Leishmania* life cycles are rodents, they are generally asymptomatic after infection or develop mild pathologies (Lainson and Shaw, 1979).