9

THE BIOLOGY OF PARASITISM

A Molecular and Immunological Approach

Editors

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Cover:

Upper Left: Stage specificity of antiparasite vaccines. See Sher, page 171.

Upper Right: Scanning electron micrograph of a *T. brucei brucei* among red blood cells. ×5500. See Donelson, page 372.

Lower Left: Separation of *Plasmodium falciparum* chromosomal DNA molecules by pulsed field gradient gel electrophoresis. Such separations provide a powerful means of mapping the parasite genome and analyzing the structure of individual chromosomes. Figure courtesy of Thomas E. Wellems, M.D., Ph.D., Malaria Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.

Lower Center: Schematic diagram showing trafficking of membrane proteins from the intracellular *P. falciparum* parasite to the RBCM. See Howard, page 137.

Lower Right: Sketch of the structure of a monomeric subunit of the MITat 1.2 VSG, based on crystallographic evidence. See Turner, page 361.

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Preface

In July 1888, the *Falmouth Enterprise* (a weekly newspaper published in Falmouth, Massachusetts) announced a new scientific establishment in "Woods Hole." The *Enterprise* article noted that the new Marine Biological Laboratory (MBL) "seeks to give advanced workers, investigators, experts, etc., opportunities for pursuing their researches in life science, in the expectation that they will thereby increase the sum of human knowledge and solve some of the great problems, which still exist about marine animals and plants."

In the one hundred years since its founding, the MBL has had notable success at offering generations of investigators the opportunity to increase the sum of human knowledge and to solve some of the great problems of life sciences. The laboratory has had an especially good track record at mounting state-of-the-art summer courses in many areas of basic biology. Internationally renowned among biologists, the courses are distinguished by their constantly evolving curricula, with course directorships turning over every five years.

Almost from the beginning, MBL summer courses have played a major role in biological research, helping to shape the disciplines of cell biology, developmental biology, and neurobiology. The nine-year-old Biology of Parasitism course, one of the youngest MBL summer courses, was founded in the hope it would make a similar contribution to parasitology.

In the late 1970s, when the Biology of Parasitism course was conceived, it was clear that the powerful new tools of molecular biology were not being applied in any serious and systematic way to the study of parasites. In part this was because of a historical (and largely gratuitous) schism between parasitology and microbiology. Additionally, the field was not well-funded compared with other areas of biomedical research.

Around 1980, research on cancer, a disease that affects 10 million people worldwide, was supported by $900 million in the United States alone. At the same time, research on schistosomiasis, which affects 200 million people and results in 700,000 deaths annually, was supported by less than $3 million worldwide.

Recognizing that the benefits of modern biology were bypassing parasitology, a number of foundations and agencies turned their attention—and their resources—to the problem. This was a wise and well-timed move. Unlike

many other biomedical problems, parasitic diseases have well-known causes. With a relatively small investment, there was hope of making a significant improvement in the lives of many hundreds of millions of people.

The MBL was chosen to host the training camp for the campaign to modernize parasitology. True, the field of parasitology is not marine in any sense, but the MBL was the appropriate place nonetheless, for a number of reasons. Perhaps most important, the laboratory has a long history of multidisciplinary programs--in education and in research. As the MBL has neither a parasitology department nor a microbiology department (nor, for that matter, *any* formal department), there was no chance that any territorial struggles would limit the scope or success of a new course. At the MBL it is relatively easy to bring together an international faculty of parasitologists, microbiologists, immunologists, molecular biologists, pharmacologists, vector biologists, entomologists, and cell biologists.

In the eight years it has been offered, the Biology of Parasitism course has fulfilled all expectations. Through 1987, the course has trained 128 students, most of whom have continued research careers in parasitology or closely related fields. A literature search in the fall of 1987 turned up more than 500 papers written by former students. In 1986, the course was described in the *ASM News* (American Society for Microbiology) as "an instrumental force in modernizing this field of research (parasitology)." Photographs of participants in the Biology of Parasitism course, 1980-1987, appear in the Appendix, pages 519-522.

We are indebted to the energetic leadership of course co-directors Alan Sher and Paul T. Englund for bringing together this volume, which makes the course lectures available to investigators, educators, and students of parasitology beyond the classrooms and laboratories of the MBL.

Harlyn O. Halvorson
President and Director
Marine Biological Laboratory
Woods Hole
February 1988

Introduction

This book is based on the Biology of Parasitism course at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. During the past eight years the course has been a major factor in the renaissance of the field of parasitology. An important reason for its influence has been its emphasis on the application of molecular biology and modern immunology to the investigation of parasites responsible for human disease. The faculty and lecturers teach not only the most important current research on parasites, but also relevant areas of basic biochemistry, immunology, and molecular biology. For nine or ten weeks each summer, sixteen outstanding students, from every part of the world, participate in this course. It serves to inspire a new group of scientists each year, and it also contributes to the field by serving as an international forum for exchange of ideas and for establishment of research collaborations. Because of the Biology of Parasitism course, the MBL is now a major intellectual center for modern parasitology.

The concept of the Biology of Parasitism course was developed in the late 1970s by Drs. Joshua Lederberg, Kenneth Warren, and Anthony Cerami. Because of the MBL's great tradition in biological sciences and summer education programs, it was considered the logical institution to host the course. Dr. Paul Gross, then Director of the MBL, gave enthusiastic support. With financial assistance from the Edna McConnell Clark and Rockefeller foundations, the MBL provided space for the course laboratory. Dr. John David of Harvard Medical School was invited to be the first Course Director.

Dr. David launched the course in the summer of 1980. Because of the enthusiasm of the faculty, the multidisciplinary nature of its curriculum, and the novelty of parasites as biological systems, the course was an instant success. Modern molecular and immunological approaches were applied, in many cases for the first time, to the study of parasites of medical importance. In subsequent years the course became widely known and the number of applications grew substantially. One measure of success of the course is that many former students have proceeded to make their own contributions to research in parasitology.

We became Co-directors of the Biology of Parasitism course in 1985. Although we were initially anxious about taking over such a highly successful enterprise, we were fortunate each summer to have a truly outstanding and exuberant faculty. Our task was also eased by the generous financial support

of the Edna McConnell Clark Foundation, the MacArthur Foundation, the Burroughs-Wellcome Fund, the Wellcome Trust, and New England Biolabs. The course is currently organized in two sections. During the first 4½ weeks the students conduct organized laboratory exercises in molecular biology, biochemistry, immunology, and membrane biology and immunochemistry of parasites. During this period they also study the biology of the major parasites and vectors. The second 4½ weeks are devoted to independent research projects that reflect the individual interests of the students. Throughout the course there are morning lectures on parasite biology and on basic molecular biology and immunology. There are also several lectures on nonparasitic infectious diseases such as leprosy and AIDS.

In 1989 the course leadership will again change hands. The new Directors, Drs. John Donelson and Carole Long, will continue to emphasize molecular biology and immunology, without neglecting parasite biology and epidemiology. With the strong support of the MBL and its new Director, Dr. Harlyn Halvorson, with continued financial commitments from the MacArthur Foundation and other funding sources, and with expanding interest in the field of parasitology, the future of the course appears to be secure.

This book, a collection of essays by current and former faculty, conveys the intellectual spirit of the Biology of Parasitism Course. We have asked each contributor to summarize major concepts in an area rather than to comprehensively review the literature or present current data. Like the Woods Hole course, the book covers a wide range of subjects and expresses many different, and sometimes conflicting, points of view. We have organized the chapters within the topics of parasite biology and disease, parasite immunology, and parasite molecular biology, biochemistry, and genetics. However, because of the multidisciplinary nature of the field, some articles are not easily categorized.

All of the contributors to this volume share with us an enormous enthusiasm for the field of parasitology and for the philosophy of the Biology of Parasitism Course. We express to them our deepest appreciation for their important contributions to this book and to their continuing support of the MBL teaching program. We hope that the book will serve as an important summary not only to present, former, and future participants in the course but also to all students of parasitology. Finally, we hope that this volume will testify to the dynamic growth and keen intellectual excitement of contemporary research on parasites.

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Contents

Contributors ix

Preface
Harlyn O. Halvorson xiii

Introduction
Alan Sher and Paul T. Englund xv

THE BIOLOGY OF PARASITES AND PARASITIC DISEASE

The Global Impact of Parasitic Diseases
Kenneth S. Warren 3

Parasitic Zoonoses
G.S. Nelson 13

Control of Schistosomiasis in Man
A.E. Butterworth 43

Biology of Amebiasis: Progress and Perspectives
Adolfo Martínez-Palomo 61

South American Trypanosomiasis and Leishmaniasis: Endemic Diseases of Continental Dimensions Affecting Poor, Neglected, and Underfunded People
Philip D. Marsden 77

Developmental Biology of *Leishmania* Promastigotes
David L. Sacks 93

Does *Trypanosoma Cruzi* Modulate Infection by Inherent Positive and Negative Control Mechanisms?
Miercio E.A. Pereira 105

***Plasmodium falciparum* Proteins at the Host Erythrocyte Membrane: Their Biological and Immunological Significance and Novel Parasite Organelles Which Deliver Them to the Cell Surface**
Russell J. Howard 111

Lyme Disease and Human Babesiosis: Evidence Incriminating Vector and Reservoir Hosts
Andrew Spielman 147

PARASITE IMMUNOLOGY

Vaccination Against Parasites: Special Problems Imposed by the Adaptation of Parasitic Organisms to the Host Immune Response
Alan Sher 169

Sporozoite Malaria Vaccines
Victor Nussenzweig and Ruth S. Nussenzweig 183

Antigens of *Plasmodium falciparum* and Their Potential as Components of a Malaria Vaccine
R.F. Anders 201

Immunity to Sexual Stages of Malaria Parasites in Relation to Malaria Transmission
Richard Carter 225

Immunity to Murine Malarial Parasites
Carole A. Long 233

Induction of Cell-Mediated Immunity as a Strategy for Vaccination Against Parasites
Stephanie L. James and Phillip Scott 249

Leprosy
Barry R. Bloom 265

Immunobiology of Nematode Antigens
R.M. Maizels and M.E. Selkirk 285

Molecular Basis for Interactions Between Parasites and the Complement Cascade
Keith A. Joiner 309

Genetic Control of Immunity to Parasite Infection: Studies of *Trichinella*-Infected Mice
Donald L. Wassom 329

PARASITE MOLECULAR BIOLOGY, BIOCHEMISTRY, AND GENETICS

Trypanosome Variant Surface Glycoprotein
Mervyn J. Turner 349

Unsolved Mysteries of Trypanosome Antigenic Variation
John E. Donelson 371

Glycolipid Membrane Anchor of the Trypanosome Variant Surface Glycoprotein: Its Biosynthesis and Cleavage
Paul T. Englund, Dale Hereld, Jessica L. Krakow, Tamara L. Doering, Wayne J. Masterson, and Gerald W. Hart **401**

Parasite Pharmacology
Ching C. Wang **413**

Gene Amplification in *Leishmania*
Stephen M. Beverley, Thomas E. Ellenberger, David M. Iovannisci, Geoffrey M. Kapler, Maria Petrillo-Peixoto, and Barbara J. Sina . . . **431**

Plasma Membrane Functions: A Biochemical Approach to Understanding the Biology of *Leishmania*
Michael Gottlieb and Dennis M. Dwyer **449**

Genetics of Malaria Parasites
David Walliker **467**

***Toxoplasma gondii* Viewed From a Virological Perspective**
E.R. Pfefferkorn **479**

***Caenorhabditis elegans*: A Model for Parasitic Nematodes**
Samuel Ward **503**

Appendix
Participants in the Biology of Parasitism course, 1980 and 1981 . . . . **519**
Participants in the Biology of Parasitism course, 1982 and 1983 . . . . **520**
Participants in the Biology of Parasitism course, 1984 and 1985 . . . . **521**
Participants in the Biology of Parasitism course, 1986 and 1987 . . . . **522**

Index **523**

THE BIOLOGY OF PARASITES AND PARASITIC DISEASE

The Biology of Parasitism, pages 3–12

The Global Impact of Parasitic Diseases

Kenneth S. Warren

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The impact of parasitic diseases on the peoples of this world is truly enormous. The protozoan and helminth organisms which cause these diseases are ubiquitous and are particularly prevalent in the vast tropical regions. Particularly hard hit by these infectious agents are children: 75% of the global population is in the developing world and approximately 50% of these more than 3 billion people are under 15 years of age; 15% are in the age group 0–4. Ninety-seven percent of all infant and child deaths occur in this latter group, and most of these fatalities are due to infectious diseases (Grant, 1983). Table 1—which ranks the bacterial, viral, protozoan, and helminthic diseases of Africa, Asia, and Latin America on the basis of prevalence, mortality, and morbidity—gives some idea of the overwhelming nature of this problem (Walsh and Warren, 1979). While diarrheal and respiratory diseases rank one and two, they are each a composite of many different infections, both viral and bacterial in etiology. Malaria ranks third and continues to increase in prevalence, mortality and morbidity because of resistance of the mosquito vectors to insecticides and the parasites to antimalarial drugs. Several of the protozoan diseases—such as African sleeping sickness caused by *Trypanosoma gambiese* and *rhodesiense*, and Kala Azar, caused by *Leishmania donovani*—are almost universally fatal unless treated. Therapy, however, is inadequate, often requiring the arsenic and antimony-containing drugs which were introduced 70–80 years ago. While often not fatal, many of the parasitic diseases are grossly disfiguring such as espundia (mucocutaneous leishmaniasis) of Latin America in which the face is gradually destroyed, and elephantiasis (bancroftian and Malayan filariasis) which causes severe distortion of the limbs and genitalia. Blinding is the major complication of onchocerciasis also known as river blindness. The vast numbers of individuals infected with hookworm, ascaris and trichuris, each accounting for almost a billion victims, suffer from often subtle forms of malnutrition, including iron deficiency. For many of these diseases diagnosis is complex and difficult and treatment is inadequate; vaccines are not now available for any human parasitic disease.

TABLE 1. Prevalence, Mortality, and Morbidity of the Major Infectious Diseases of Africa, Asia, and Latin America, 1977–1978[a]

Infection	Infections (thousands/yr)	Deaths (thousands/yr)	Disease (thousands of cases/yr)	Average No. of days of life lost (per case)	Relative Personal Disability[b]
Diarrheas	3–5,000,000	5–10,000	3–5,000,000	3–5	2
Respiratory infections		4–5,000		5–7	2–3
Malaria	800,000	1,200	150,000	3–5	2
Measles	85,000	900	80,000	10–14	2
Schistosomiasis	200,000	500–1,000	20,000	600–1,000	3–4
Whooping cough	70,000	250–450	20,000	21–28	2
Tuberculosis	1,000,000	400	7,000	200–400	3
Neonatal tetanus	120–180	100–150	120–180	7–10	1
Diphtheria	40,000	50–60	700–900	7–10	3
Hookworm	7–900,000	50–60	1,500	100	4
South American trypanosomiasis	12,000	60	1,200	600	2
Onchocerciasis					
Skin disease	30,000	Low	2–5,000	3,000	3
River blindness		20–50	200–500	3,000	1–2
Meningitis	150	30	150	7–10	1
Amebiasis	400,000	30	1,500	7–10	3
Ascariasis	800,000–1,000,000	20	1,000	7–10	3
Poliomyelitis	80,000	10–20	2,000	3,000+	2
Typhoid	1,000	25	500	14–28	2
Leishmaniasis	12,000	5	12,000	100–200	3
African trypanosomiasis	1,000	5	10	150	1
Leprosy		Very low	12,000	500–3,000	2–3
Trichuriasis	500,000	Low	100	7–10	3
Filariasis	250,000	Low	2–3,000	1,000	3
Giardiasis	200,000	Very low	500	5–7	3
Dengue	3–4,000	0.1	1–2,000	5–7	2
Malnutrition	5–800,000	2,000			

[a]Based on estimates from the World Health Organization and its Special Programme for Research and Training in Tropical Diseases, confirmed or modified by extrapolations from published epidemiologic studies performed in well defined populaitons (see references). Figures do not always match those officially reported, because undereporting is great.

[b]1 denotes bedridden; 2, able to function on own to some extent; 3, ambulatory; 4, minor.