

3rd International Symposium on:  
The Biochemistry of Parasites and  
**THE** Host-Parasite Relationships  
**HOST-INVADER**  
**INTERPLAY**

H. Van den Bossche Editor

# THE HOST-INVADER INTERPLAY

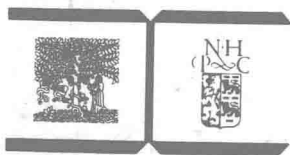
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## PREFACE

### Scene Setting and Objectives

Infections remain the greatest unsolved problem facing mankind. The number of people who risk infection with African trypanosomiasis is on the order of 35 million. This form of trypanosomiasis causes sleeping sickness in man and nagana in cattle. Nagana is probably the main barrier to the development of extensive beef production in Africa and is the main obstacle to economic development of 10 million square kilometers of Africa. Another form of trypanosomiasis, known as Chagas' disease, is widespread in Central and South America. The estimated number of infected humans in Latin America amounts to 7 million.

The muco-cutaneous forms of leishmaniasis cause severe mutilation and suffering in South America. Visceral leishmaniasis, or kala-azar, fatal within two years if not treated, appears to be increasing in incidence in East Africa.

Diarrheal diseases are common and important in most tropical countries, they may be caused by bacteria, viruses or by the protozoa *Giardia lamblia* or *Entamoeba histolytica*.

In Africa, about one-fourth of all adults suffer from malarial fever at one time or another. At least one million children die of the disease each year. In Africa and Asia at least 400 million people are currently considered to be at risk of becoming infected.

At least 20 million people living in tropical Africa are infected with *Onchocerca volvulus*, the worm that causes river blindness. Onchocerciasis has restricted access to land and other resources in parts of Africa. Not less than 300 million people are infected with *Wuchereria bancrofti* an infection that can lead to elephantiasis, inflicting suffering on millions of people.

Schistosomiasis, a parasitic disease caused by worms living in the blood, is endemic in tropical regions of Africa, Asia, South America and the Caribbean Islands, affecting 200 million to 300 million people.

These, and even more impressive figures on hookworm disease, trichuriasis, ascariasis and mycotic infections are estimates used to bemoan the sad state of the developing world and/or to plead for better conditions in the developing countries for the utilization of existing drugs. These figures have also been used to evaluate the causes of such suffering; to search for answers to questions as: why should millions of people be parasitized? Why did scientific research

not lead to eradication or even reduction of these diseases? What is the principal obstacle preventing, for example, the development of a successful sleeping sickness and/or chemotherapeutic agent?

Many assume that this originates from an inadequate funding of research on tropical diseases or from an insufficient number of informed scientists. Obviously, funding and motivated scientists are needed. The presence at this symposium of such a great number of scientists, of the highest international standing, all aware of the vital importance of research for the development of new remedies indicates that the lack of good people is not the main reason for the slow improvement of the situation. To paraphrase C. de Duve, lack of money and good people is not the explanation of the failure to find a cure for cancer.

To my mind a main reason lies in the invading cells and organisms themselves. Tumour cells, bacteria, yeasts, fungi, protozoa and helminths all have developed a huge number of mechanisms to escape from the clutches of their host's defence systems. For example, trypanosomes survive in the bloodstream of the host by periodically altering their antigenic profile. Schistosomes may cover their teguments with glycoproteins that appear to be copies of host proteins. In fact, they become wolves in sheep's clothing.

We have to learn more about the metabolic, chemical and physical mechanisms involved before we can offer remedies to attain a large measure of disease control.

The main objective of this symposium was to evaluate the present state of knowledge. The understanding of the host-parasite interactions which determine the invasive behaviour of a cell or organism requires knowledge of its surface properties. A number of papers on topochemistry, ultrastructure and dynamics of the surface served as introduction to the discussion of the invasive mechanisms and of interactions at the interface level between host cells and invaders. Mechanisms utilized by invasive cells and organisms to avoid destruction by the host defensive systems were reviewed. Part of the symposium was devoted to analyse subversive activities of invasive organisms. Factors determining the pathogenicity were discussed. The association of eosinophils, neutrophils, macrophages and mast cells with parasitic diseases was evaluated. Finally, the prophylactic and therapeutic methods available and needed to eliminate the uninvited guests were analyzed.

It is hoped that this book, which is comprised of the papers presented at the symposium, will extend the horizon of knowledge, will make discoveries possible and prepare the way for new applications.

I take this opportunity to thank Dr. Paul Janssen for providing the opportunity to organize this symposium and for the suggestion to include studies on

tumour cells, bacteria and yeasts in the programme.

In particular I would like to thank M. Müller who already in June 1978 stood at the cradle of this symposium, K.S. Warren who suggested the name, B.A. Newton for generously offering to prepare the summary and outlook and the other members of the scientific committee W.K. Amery, J. Barrett, M. Borgers, A. Capron, B. Ogilvie, W. Peters, A.W. Senft and D. Thienpont for their advice and constructive criticism throughout the organization of this symposium.

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Last but not least I would like to thank Jeannine, Piet and Hilde for their tolerance and encouragement during the preparation of this symposium and book.

Hugo Van den Bossche

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## THE HOST/"PARASITE" INTERFACE





## CELLULAR MEMBRANES AND THE HOST-PARASITE INTERACTION

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### ABSTRACT

This paper treats host/parasite interfaces recognized in leishmaniasis, S. American trypanosomiasis and malaria. The interfaces considered are those between extracellular forms and the extracellular fluid, extracellular forms and macrophages, malaria merozoites and red cells and between malaria-parasitized red cells and the host. Parasite-induced host erythrocyte modifications during the red cell cycle of malaria constitute the major focus. Metabolic labeling, surface-labeling of intact parasitized cells, fractionation of parasitized cells and analysis of the pure host-cell membranes by immune precipitation and electrophoresis, crossed immune electrophoresis, isoelectric focusing and dodecyl sulfate polyacrylamide gel electrophoresis have provided important information about parasite-synthesized host cell neoproteins. In *P. knowlesi*-infected erythrocytes the dominant neoprotein is a  $\sim 65,000$  pI 4.5 glycoprotein that is naturally immunogenic.

### INTRODUCTION

Vertebrate cycles of parasitic protozoa involve programmed, progressive and sometimes alternating changes in the structures, surface properties and compartmentalization of the parasites. These remarkable adaptations represent features of parasite-host interplay that are enacted largely at plasma membranes of parasites and/or host cells, and become striking in malaria where the membrane of host erythrocytes incorporates parasite generated proteins.

### PARASITE/EXTRACELLULAR FLUID INTERFACES

*Plasmodia*, *Leishmania* and *T. cruzi*, protozoans that are primarily intracellular parasites, in their vertebrate hosts pass through extracellular stages, that are specialized for transit between different locations. These intermediate stages might be expected to be targets for immune attack because they lack the protection of a host cell plasma membrane. However, the extracellular forms of protozoan parasites generally possess features that make them inconspicuous and reduce their vulnerability. Surface coats are prominent, may prevent access to the parasite per se, of deleterious extracellular-fluid components (enzymes,  $\text{Ca}^{2+}$ , antibodies) and can absorb extracellular-fluid proteins to produce a host-like surface. True antigenic mimicry, i.e. incorporation of host histocompatibility antigens as occurs with Schistosomes<sup>1</sup> has not been proven for the protozoan parasites. However, in chronic *T. cruzi*



infections, small numbers of parasites consistently occur in the blood and the possibility exists that these represent a population displaying antigenic compatibility with the host or even antigenic mimicry<sup>2</sup>. The advantage of antigenic mimicry, obviously significant in blood-dwelling metazoans, appears less great for protozoan parasites.

Merozoites are the plasmodial forms infectious for red cells and those of some species of Plasmodium can be recognized as foreign by their hosts<sup>3,4</sup>. Antibodies in sera from adult Gambian patients immune to P. falciparum, but never exposed to P. knowlesi, bind to the surfaces of intact P. knowlesi merozoites<sup>3</sup> and [<sup>125</sup>I]-labeled surface proteins on these merozoites form complexes with the patients' antibodies. Triton X-100 extracts of P. falciparum schizonts inhibit the reaction of the patients' antibodies with P. knowlesi merozoites. The antibodies do not block invasion of susceptible red cells. The data demonstrate that merozoites can be immunologically vulnerable and indicate immunologic cross-reactivity between two species of primate malaria. The results do not inform about the importance of merozoite antigens, in terms of protective immunity, relative to other plasmodial antigens.

Studies with monoclonal antibodies document the antigenicity of P. yoelii merozoites<sup>4</sup>. Spleen cells from P. yoelii mice, fused with mouse myeloma cells, generate hybrid cells that yield P. yoelii-specific antibody. About half of the hybridoma cultures tested produced anti-merozoite antibody, as determined by indirect immune fluorescence, and half antibody directed against the membranes of infected erythrocytes. The anti-merozoite antibody, cross-reacted with merozoites of another rodent malaria (P. V. petteri), suggesting possible stage specificity. When transferred to non-immune mice, the anti-merozoite antibody conferred protection against infections with virulent strains of P. yoelii. The ultimate recovery of the mice treated with the monoclonal antibodies appeared to be mediated by the recipients' own antibodies, rather than the transferred immunoglobulin. It is hypothesized, but not tested in contrast to Miller et al<sup>3</sup>, that the recipients' antibodies may block host cell invasion. The results document the immunological vulnerability of P. yoelii merozoites, but do not provide information about merozoite immunogenicity. They do not indicate that protective immunity against all malarias is mediated exclusively by anti-merozoite antibodies.

Plasmodial sporozoites are the forms that populate the saliva of infected mosquitos and are infectious for vertebrate hosts. Immunization of mice<sup>5</sup> and rhesus monkeys<sup>6</sup> with radiation-inactivated sporozoites of P. berghei and P. knowlesi, respectively, produces a stage-specific host immunity detected by