Immunity to parasites

How parasitic infections are controlled

SECOND EDITION

DEREK WAKELIN

D.Sc., F.R.C. Path., Professor of Zoology, University of Nottingham

CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge CB2 1RP, United Kingdom

CAMBRIDGE UNIVERSITY PRESS
The Edinburgh Building, Cambridge CB2 2RU, UK http://www.cup.cam.ac.uk
40 West 20th Street, New York, NY 10011-4211, USA http://www.cup.org
10 Stamford Road, Oakleigh, Melbourne 3166, Australia

First published 1984 by Edward Arnold
Second edition published by Cambridge University Press 1996
Reprinted 1998

Printed in the United Kingdom at the University Press, Cambridge

Typeset in Monotype Garamond 11/13pt, in QuarkXPress™ [SE]

A catalogue record for this book is available from the British Library

Library of Congress Cataloguing in Publication data

Wakelin, Derek.
Immunity to parasites : how parasitic infections are controlled / Derek Wakelin.
p. cm.
Includes bibliographical references.
ISBN 0 521 56245 7 (hardcover). – ISBN 0 521 43635 4 (pbk.)
1. Parasitic diseases – Immunological aspects. I. Title.
QR201. P27W35 1996
616.9′6079–dc20 95-48213 CIP

ISBN 0 521 56245 7 hardback
ISBN 0 521 43635 4 paperback

Contents

1

Parasites and parasitism

The host as an environment

1.1 Introduction

In many older textbooks of zoology it was customary to treat parasite species as though they were in some way quite separate from free-living animals. The term 'degenerate', which was used to describe the apparent simplifications in structure shown by parasites when compared with their free-living relatives, also carried with it a whiff of moral disapproval for their way of life! Today the pendulum has swung almost to the other extreme and parasitism is sometimes represented as nothing more than another form of environmental exploitation. It is indeed a remarkably successful exploitation and one that has been a major ine of evolutionary development in several phyla. The success of this way of life is attested by the ubiquity of parasites, in hosts of every phylum, and in the long-term stability of many host–parasite relationships. In essence, of course, it is true that exploitation of the host environment is very similar to the exploitation of any other environment, but there is one very important difference. Unlike the environments of free-living animals, the environment provided by a host can respond adaptively to the presence of a parasite. It is this difference, the adaptive interaction of host and parasite, each concerned with its own evolutionary survival, that distinguishes parasitism from other modes of life.

1.2 What is a parasite?

Despite the distinctive feature outlined above it is almost impossible to define parasitism in terms that completely exclude related modes of interspecific

association such as commensalism and mutualism. In the host–parasite relationship the parasite is undoubtedly the beneficiary, but the precise requirements for parasite survival and the extent to which the host may suffer from the association are extremely variable. For the purposes of this book, which will be concerned almost exclusively with endoparasites in warm-blooded hosts (Table 1.1), it is useful to apply some ecological concepts in describing the essential characteristics of the parasitic way of life.

For parasites the host is the total environment. Larval and other reproductive stages may live in the outside world for longer or shorter periods but this represents merely a necessary phase in the movement from host to host. Particular parasites occupy particular niches in the major habitats provided by the host environment and are adapted to the conditions present in those niches in exactly the same way as free-living organisms are adapted to their environments. Although the environment is wholly biotic in origin, as it is provided by a living organism, it is still possible to define each niche by what are essentially abiotic factors such as pH, oxygen tension, redox potential and nutrient availability, as well as truly biotic factors such as other parasites and resident microorganisms. The ecological analogies break down, however, when one considers that the environment provided by the host is not passive, but can react adaptively to the presence of the parasite. Thus even in an environment to which they are perfectly adapted, parasites are faced by a variety of potentially destructive factors never experienced by free-living species, for example antibodies, complement, cytotoxic cells, lysosomal enzymes, and toxic metabolites as well as predatory phagocytic cells. The ability of the parasite to evade or resist these adaptive responses ultimately determines the ability of the parasite to survive and reproduce.

An important consequence of the endoparasitic condition is that the parasite is cut off from direct experience of the external world. Some parasites still rely on external changes in temperature and day length, which they detect indirectly through the hormonal and other changes in the host, to control their own developmental processes. Others (e.g. intestinal nematodes of sheep) use their direct experience of these changes, whilst they are in the external world as larval stages, to regulate their development after entry into the host. The majority coordinate their growth, development and reproduction by responding to factors present within the host environment that have little or no relationship to the outside world. Such adaptations have clear selective advantage in preventing developmental changes from taking place in the absence of suitable hosts.

Table 1.1 *Table of major parasites referred to in the text*

Classification	Genus	Position in host	Transmission	Size
Protozoa				
Mastigophora	*Trypanosoma*	Extracellular/Blood	Bite of tsetse fly	15–25 μm
	Leishmania	Intracellular/Macrophage	Bite of sandfly	2–5 μm
Apicomplexa	*Plasmodium*	Intracellular/RBC	Bite of mosquito	2–20 μm
Platyhelminthes				
Digenea	*Schistosoma*	Blood vessels (adults)	Skin penetration by larvae	10–30 mm (♀)
Nematoda				
Strongylida	Hookworms, *Haemonchus, Nippostrongylus, Trichostrongylus, Heligmosomoides*	Intestinal lumen	Oral ingestion or skin penetration by larvae	10 mm (♀)
	Dictyocaulus	Lungs		10 cm (♀)
Trichinelloidea	*Trichinella*	Intracellular/Gut epithelium	Oral ingestion of larvae	2–3 mm (♀)
Filaroidea	*Wuchereria, Brugia*	Lymphatics (adults)	Bite of mosquito	100 mm (♀)
	Onchocerca	Subcutaneous tissue (adults)	Bite of *Simulium*	500 mm (♀)
Arthropoda				
Acarina	'Ticks'	Ectoparasitic on skin	Direct host contact	5–15 mm (♀)

1.3 Parasites and parasite life cycles

1.3.1 Parasites

Animals that live as parasites occur in almost every phylum and animals of every phylum are subject to parasitic infection; the total number of parasite species is therefore enormous. Even if consideration is restricted only to parasites affecting humans and domestic animals, the number of species known is very large, yet for the majority, little or nothing is known of immunological aspects of their relationships with their hosts. Our present understanding of immunoparasitology comes from studies made on relatively few species and we have to assume that this understanding will prove to have general applicability. Table 1.1 includes some of the parasites that have been studied in detail, either because they are of clinical or veterinary significance, or because thay provide useful experimental models. The genera listed belong to the four major parasitic groups – Protozoa, Platyhelminthes, Nematoda and Arthropoda – and cover a wide size range, from very small intracellular parasites to very large extracellular worms, which may be several thousand times larger. It is useful to divide the groups into two major categories – *microparasites* (protozoans) and *macroparasites* (platyhelminths, nematodes and arthopods) – not only in terms of their size, but also in terms of their ability to increase numbers by replication within the host. Protozoans, together with the other major microparasites, viruses and bacteria, replicate within the host, and levels of infection can rise rapidly even after a single infection event, which, theoretically at least, need involve only a single organism. In contrast, the majority of macroparasites cannot replicate within the host, and levels of infection are determined by the number of infection events and the number of infective stages acquired. This biological distinction between micro- and macroparasites is therefore of fundamental importance in both epidemiology and immunoparasitology.

1.3.2 Life cycles

There is an almost infinite variety of ways in which parasites reach their hosts and of life cycles directed to this end, but it is possible to reduce this variety to a number of basic patterns.

(*a*) The parasite is never exposed to the external world and completes its development and reproduction in a single host. Transmission between

hosts is normally achieved by predation or scavenging (Fig. 1.1a). Relatively few parasites show this pattern.

(*b*) The parasite is never exposed to the external world, but its development cycle takes place in two or more host species. The species in which the parasite reaches sexual maturity is known as the *final* or *definitive* host: that in which larval, juvenile or non-sexual stages develop is known as the *intermediate* host. Where one host transmits the parasite directly to another it is also referred to as a *vector* and this term is applied particularly to arthropods (Fig. 1.1b).

(*c*) The parasite is exposed to the external world for varying periods of time, but does not have active, free-living stages. The infective forms are contained within protective structures such as cysts (Protozoa) or egg shells (Nematoda). The life cycle may be *direct* in that only one host species is involved, or *indirect*, involving intermediate and final hosts of different species (Fig. 1.1c).

(*d*) The parasite is exposed to the external world as an active, free-living form during its development and transmission between hosts. Re-entry into the host may be a passive process, i.e. by ingestion, or an active process by penetration. As before, the cycle may be direct or indirect (Fig. 1.1d).

In all patterns, certain phases in the life cycle act as the infective stages and these may show well-defined morphological or physiological adaptations for this function. These are particularly evident in the skin-penetrating larvae of helminths, for example the cercariae of schistosomes, which possess suckers for adhesion and a battery of glandular structures that release histolytic enzymes. Characteristic of all infective stages is the capacity to recognize the host environment. In protozoan infective stages such as the malarial sporozoite, this capacity operates at a molecular level and involves complementarity between molecules present on the parasite and molecules expressed on host cell membranes. In the infective stages of helminths, particularly those that enter the host in a protective sheath, cyst or eggshell, recognition of the host involves response to certain physico-chemical stimuli that act as triggers to initiate escape from the protective layers and recommencement of growth and development. Clearly, despite numerous adaptations to ensure that it is the correct host species that is invaded, there is a large random element in the process. Host contact may or may not be made. If made, infection may fail because the host is unsuitable. The reasons underlying failures of the latter kind can be very instructive because, by throwing light upon the phenomenon of natural resistance or natural insusceptibility to infection, they reveal much about the characteristics of the susceptible host.

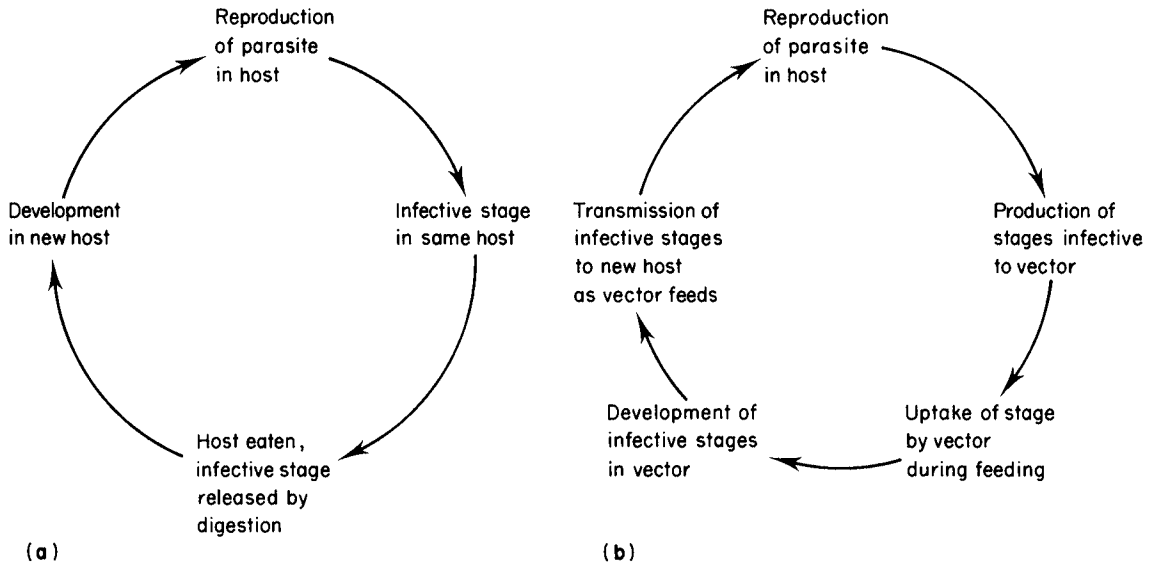

Fig. 1.1 Life cycles of endoparasites.
(a) Direct cycle, parasite never exposed to the outside world, transmission by carnivory, e.g. *Trichinella* (Nematoda).
(b) Indirect cycle, parasite never exposed to the outside world, transmission by arthropod vector, e.g. *Plasmodium* (Protozoa), *Wuchereria* (Nematoda).

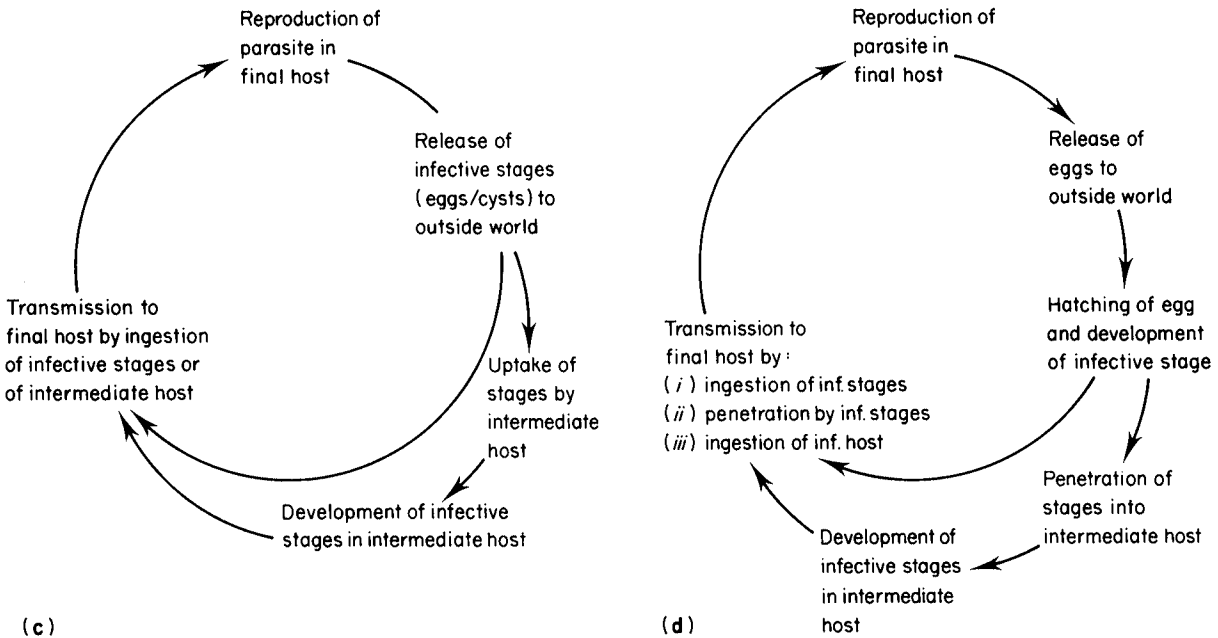

Fig. 1.1 (cont.)
(c) Direct and indirect cycles, parasite exposed to the outside world but not as an active free-living stage. Transmission direct, e.g. *Toxoplasma* (Protozoa), *Ascaris* (Nematoda), or indirect via an intermediate host, e.g. tapeworms (Platyhelminthes).
(d) Direct and indirect cycles, parasite exposed to the outside world as free-living stage. Transmission direct, e.g. hookworms, *Haemonchus* (Nematoda), or indirect via an intermediate host, e.g. *Schistosoma* (Platyhelminthes).

Table 1.2 *Influence of factors involved in natural resistance and acquired resistance to parasitic infection*

Stage in host parasitic infection	Host characteristics that influence interaction			
	Behaviour	Structure	Physiology	Immunity
Initial contact	+	+	–	–
Establishment in host	–	+	+	–
Development of parasite	–	+	+	+
Reproduction of parasite	–	–	+	+

Notes:
Natural resistance is expressed through the host's behaviour, structure and physiology; acquired resistance is expressed through the host's immune response. The two categories are not absolute, each is intimately related to the other.

1.4 Natural resistance to infection

Natural resistance is a phenomenon operating at many levels (Table 1.2). Hosts can be considered naturally resistant to parasites because, through geographical distribution, behavioural characteristics or nutritional habits, they simply do not come into contact with infective stages. (Our natural resistance to may parasites is clearly of this kind and all too frequently breaks down.) Natural resistance more conventionally encompasses a physiological incompatibility between parasite and host environment that prevents invasion, establishment or survival without the intervention of immunologically based protective responses. For example:

(*a*) Helminths, such as schistosomes and hookworms, that rely on skin-penetrating larvae for infection may be unable successfully to cross the epidermis and basement membrane in order to enter the dermis.
(*b*) Trypanosomes entering the blood may be killed by factors naturally present in serum, such as the high density lipoprotein that destroys animal-infective *T.b. brucei* in humans, or may activate complement and be lysed.
(*c*) Intracellular protozoa such as *Plasmodium* may be unable to enter host cells because these lack essential surface molecules.
(*d*) Parasites that enter the host orally and which require activation by specific triggers in the intestinal environment may not experience these factors or the correct combination of factors that is necessary.

Even if the host provides an environment suitable for initial development, incompatibilities may well arise at subsequent stages through nutritional inadequacies, or through incomplete stimuli for migration and reproductive maturation. The eggs of the human *Ascaris*, *A. lumbricoides*, for example, can hatch in a variety of mammalian hosts because of the relatively low specificity of the intestinal signals required (mammalian body temperature, alkaline pH, dissolved CO_2 and a reducing environment). After hatching, the larvae can migrate and reach the lungs but development after this point, and sexual maturation, occur only in humans. It follows from this that, in natural host–parasite relationships, the parasite must be precisely adapted to the structural and physiological conditions that characterize the host species. This adaptation, which develops over long periods of evolutionary change, is the basis for the phenomenon of host specificity, i.e. the restriction of parasites to particular speces of hosts. In some cases the restriction is near absolute, as occurs with the human malaria parasites and certain of the human filarial nematodes. In other cases the restriction is extremely loose and parasites can undergo development in, and be transmitted between, a wide variety of hosts, as occurs with the nematode *Trichinella spiralis*. For the majority of parasites host specificity falls between these extremes and under natural conditions particular species are found in only a few species of hosts.

1.5 Acquired resistance to infection

In host–parasite relationships where natural resistance is low, the host can regulate the degree of infection to which it is subject only through the activities of its immune system, that is by developing an acquired resistance to infection. The degree to which such regulation operates, or indeed is necessary, under natural conditions is an open question and one for which few data are available. It is conceivable that in the wild, rates of transmission are such that parasite burdens remain below the thresholds necessary for the stimulation or expression of immune responses. With protozoan infections, of course, this factor is then offset by the parasite's ability to reproduce within the host. Rates of transmission are determined by a number of environmental factors, of which host density is one of the most important. It is the alterations of these factors, which humans impose upon themselves and their domestic animals, that lead to increased rates of transmission, increased prevalence and intensity of infection thus emphasizing the role of acquired immunity in control. Even where it is obvious that acquired immunity is necessary, the degree to which the host succeeds in regulating infection in this way

is very variable. Many parasites have evolved successful means of evading the immune response that they evoke and some seem not to evoke protective responses at all. Others depend for their survival as a species on development and reproduction within individual hosts that are, for various reasons, incapable of developing or expressing an adequate protective immunity.

Implicit in the concepts of host specificity and of balanced relationships is the assumption that the ability of the host to control the parasite is never absolute. Several workers have put forward the concept that in evolution there is always a tendency towards a mutual adjustment between the two species, the parasite reducing its pathogenicity and immunogenicity so as to elicit weaker host responses, the host reducing its responsiveness so that parasite control is achieved without concomitant pathological change. 'Successful' parasites therefore tend to become harmless to the host. An example frequently cited in support of this concept is the relatively benign association of trypanosomes in game animals compared with the pathological consequences of human infections. Whether this interpretation is of general applicability is open to question. Many associations are still remarkably pathogenic for the host, in others the host rapidly achieves control of the parasite. Although it seems self-evident that mutual adjustment is necessary for mutual survival there are many parasites, particularly those transmitted through food chains, for which death or incapacity of the host can only facilitate their own transmission. It is, in fact, likely that there is no single trend in the evolution of host–parasite relations and that a variety of endpoints may be achieved, however three factors in particular suggest that the host–parasite relationship is always a confrontation for survival. One is the variability within species of the mechanisms controlling natural and acquired resistance. This implies the operation of strong selective pressures from infectious organisms. The second is the very existence and complexity of the resistance mechanisms possessed by all animals, but particularly by vertebrates. It is hard to see why such elaborate devices should have evolved, and why they should have persisted, if they did not confer powerful selective advantages. The third is the evidence of substantial genetic variability within parasite populations, which attests to the effectiveness of selection pressures exercised by host resistance.