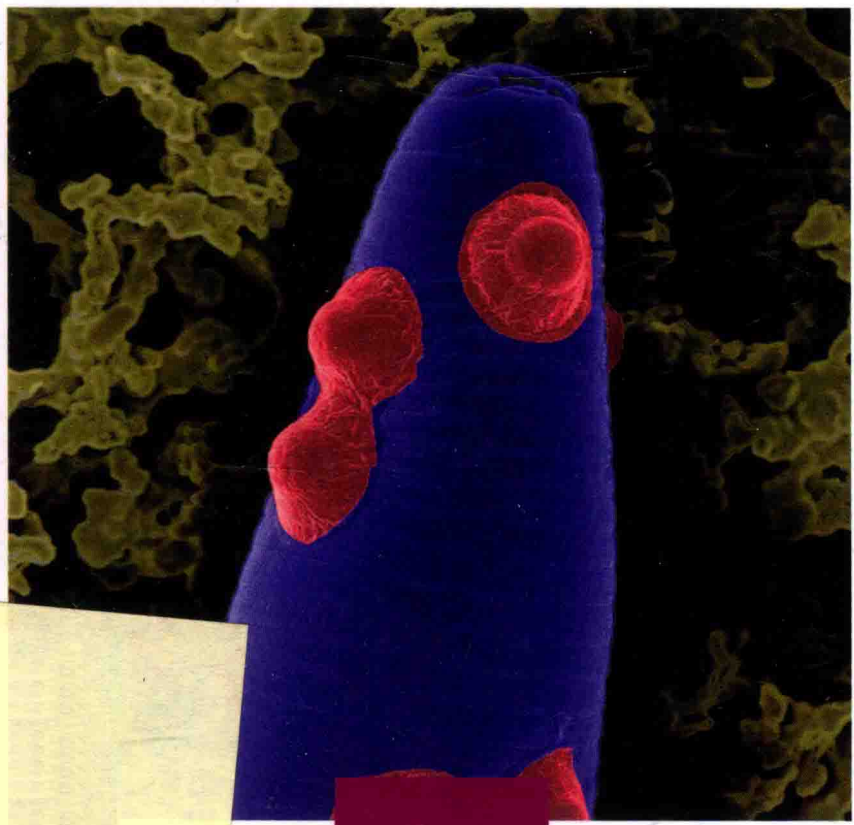
ADVANCES IN PARASITOLOGY

Natural History of Host–Parasite Interactions



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Natural History of Host–Parasite Interactions

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PREFACE

This thematic volume of *Advances in Parasitology* was conceived as a result of a symposium held at the Linnaean Society in the autumn of 2007, for which I had the pleasure to convene together with Dr David Rollinson, to mark the tercentenary of Linnaeus's birth in combination with the Centenary celebrations of both Imperial College and the Royal Society of Tropical Medicine and Hygiene. The symposium was extremely successful and highly attended, and we were delighted that almost every speaker was willing to subsequently contribute their papers to this volume.

Dobzhansky wrote in his famous essay, "Nothing in biology makes sense except in the light of evolution", yet this truth so often appears to be ignored within the medical and biomedical disciplines. Evolution and co-evolution are the foundations of biology, and biology is the foundation of medicine and public health. For example, co-evolution has epidemiological implications, particularly in the context of emerging and re-emerging diseases. If co-evolution imposes constraints on susceptibility and pathogenicity, those constraints may no longer hold when new host-parasite associations emerge or ancient associations are disrupted, affecting both the magnitude and severity of disease outbreaks. There may also be indirect effects of changes in the range of parasites to which a host population is exposed through altering the selection pressures on existing parasites. Likewise, altering host genetics, especially by selective breeding for resistance to a particular parasite, could also affect selection pressures on other parasites. Understanding how parasites respond to evolved changes in host characteristics may also provide a good model for their all too apparent potential to respond to other kinds of change, such as the use of new drugs or vaccines to combat disease. Evolutionary theory has, therefore, an important role to play in both the interpretation of host and parasite dynamics and the design and application of disease control programmes.

This volume brings together a range of articles from scientists from different fields of research and/or disease control, but with a common interest in studying the biology of a variety of parasitic (in its broadest sense) diseases. In so doing, we aim to present what evolutionary thinking can contribute to an integrated understanding of the processes shaping host-parasite interactions and control.

Katrin Hammerschmidt and Joachim Kurtz's paper considers host-parasite interactions in parasites with complex life cycles, and hence those that require two or more consecutive invertebrate and vertebrate hosts. Despite the fact that so many parasites, including those of profound medical and veterinary importance, have complex life cycles, our understanding of the evolution of complex life cycles is currently still in its infancy. This paper describes in detail recent research into the immunological interaction of such a parasite, the model tapeworm *Schistocephalus solidus*, with its two intermediate hosts, a cyclopoid copepod and the three-spined stickleback. The data presented indicate that immunological interactions between host(s) and parasite(s) are relevant factors influencing not only parasite establishment and growth, but potentially also behavioural manipulation of the hosts. In complement to the Lefèvre *et al.* paper above, these authors elaborate upon the "extended phenotype" concept to include the proximate physiological causes, whereby parasitised hosts can truly be seen as "deeply modified organisms".

Turning towards more field-based evolutionary and epidemiological studies, Judith Smith examines one of our most ubiquitous parasites, *Toxoplasma gondii*. The paper describes how this parasite's, again complex, life cycle has become adapted to exploit multiple routes of transmission through a sexual cycle in the definitive host and asexually in the intermediate host. While such alternative routes may operate synergistically to enhance transmission, this paper illustrates how they might also provide a vehicle for selection, leading to partitioning of strains in the environment, including potential differences in shifts from sexual to asexual transmission between epidemiological regions.

Alison Dunn's review considers the fate of (non-human) parasites during a biological invasion and their impact on both native and invasive hosts, asking whether parasites can directly or indirectly mediate invasion success. Using illustrations from a range of studies focusing on parasitism in amphipod invasions, this paper describes how, for example, an introduced species may either lose its parasites as a result of the introduction, introduce novel parasites to hosts in the new range and/or acquire parasites from its new environment. Furthermore, this paper highlights how, as a result of local adaptation, parasites tend to have a differential effect on native versus invading hosts, which will be a key determinant for the outcome of any invasion and its impact on the recipient community.

Fiona Mathews' paper then considers the importance of a detailed understanding of the ecology of zoonotic diseases in wildlife, both in terms of predicting their success and managing their control. More than two-thirds of emerging, or re-emerging, infectious diseases are thought to

originate in wildlife. Despite this, co-ordinated surveillance schemes are rare, and most efforts at disease control operate at the level of crisis management. This review examines the pathways linking zoonoses in wildlife with infection in other hosts, using examples from a range of key zoonoses including European bat lyssaviruses and bovine tuberculosis. The paper also describes how, while the vast majority of efforts to control zoonoses in wildlife hosts rely on culling strategies, the alternative, and potentially more successful, approach is to understand the factors leading to disease outbreaks in the first place and to manage these instead.

Issues of the importance of understanding host-parasite interactions for disease control, in this case biocontrol by a bacterium *Pasteuria penetrans*, a hyperparasite of root-knot nematodes (*Meloidogyne* spp.), are also illustrated in the paper by Keith Davies. It is only relatively recently with the development of industrialised agriculture that plant parasitic nematodes have been recognised as an important constraint on crop production. For the majority of their evolutionary history, plant parasitic nematodes have been part of a multi-trophic interaction between their plant host and their natural enemies. This paper discusses the reasons why bacterium-nematode surface interactions are likely to hold the key to understanding host-specificity and evolutionary dynamics in this system, and presents some genomic insights into potential solutions for future bio-control.

In terms of direct disease control of human parasites (and hence where public health measures can be seen as a major interaction by a host on their parasites), Alan Fenwick's paper documents how recent shifts in global health policy have led towards the implementation of mass chemotherapeutic control programmes at the national scale in previously 'neglected' countries, such as those within sub-Saharan Africa. However, while celebrating the rapid success achieved to date by such programmes, in terms of reduced infection prevalence, intensity and associated human morbidity, it is acknowledged that evolutionary change in response to drug selection pressure may be predicted under certain circumstances, particularly in terms of the development of potential drug resistance. Theoretical and empirical data gained to date thereby serve to highlight the importance of careful monitoring and evaluation of parasites and their hosts whenever and wherever chemotherapy is applied and where parasite transmission remains.

The paper by María-Gloria Basáñez and colleagues then focuses on one of these neglected tropical diseases, onchocerciasis, in relation to its blackfly (*Simulium*) vector, with particular reference to the transmission dynamics, density-dependent interactions, evolutionary implications and ultimately control of human onchocerciasis. The authors examine

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CHAPTER 1

HLA-Mediated Control of HIV and HIV Adaptation to HLA

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weeks by 10^2-10^3 copies per ml of plasma to a relatively stable viral set-point with a median of around 30,000 copies per ml. The particular set point established in each individual HIV-infected person is strongly predictive of the time it will take for that person to progress to AIDS; lower viral set-points predict slower progression to AIDS and higher viral set-points predict more rapid progression (Mellors *et al.*, 1996). For instance, a viral set point of 30,000 copies per ml of plasma is predictive of AIDS progression in approximately 10 years in the absence of ART.

There are several lines of evidence to indicate the central role of CTL in control of HIV replication. First, the temporal association between the appearance of HIV-specific CTL responses and the decrease in viral load during acute infection suggests the importance of CTL in the establishment of viral set-point (Borrow *et al.*, 1994; Koup *et al.*, 1994). This observation was confirmed by studies in the Simian Immunodeficiency Virus (SIV)-macaque model, in which depletion of circulating CTL with anti-CD8 monoclonal antibodies resulted in a loss of control of viraemia in both the acute and chronic phase (Jin *et al.*, 1999; Matano *et al.*, 1998; Schmitz *et al.*, 1999).

A second line of evidence to support the role of CTL in immune control of HIV is the association between certain HLA class I molecules and disease outcome (Carrington and O'Brien 2003; Goulder and Watkins 2008; Kiepiela *et al.*, 2004). CTL are able to recognise HIV-infected target cells because the infected cells present fragments of HIV proteins in the peptide-binding groove of cell-surface HLA class I molecules. Recognition of the HIV peptide/HLA complex on the target cell, by the T-cell receptor (TCR) of the CTL results in the release of cytokines, chemokines and molecules, such as perforin and granzymes, that affect the rapid lysis and apoptosis of the infected target cell. The HLA region, which is situated on the short arm of chromosome 6, is the most polymorphic of the entire human genome (Mungall *et al.*, 2003). This extraordinary diversity ensures that a wide range of pathogen-derived proteins can be presented for recognition by CTL. The disease outcome from HIV, and other infectious diseases that are contained by CTL, is thus critically dependent on the particular protein fragments presented by HLA class I molecules. Which HIV proteins form successful targets for CTL and which form apparently useless targets for CTL is further discussed below.

In the context of HIV, the reason that different HLA molecules can be associated with particular disease outcomes may be due to differences in the peptide-binding groove of the HLA molecules and hence the different fragments of HIV peptides that are presented for recognition by CTL. For example, HLA-B*57, which is associated with successful control of HIV infection, typically binds peptides that carry either a tryptophan or a phenylalanine (both large, hydrophobic residues) at the carboxy-terminus of the peptide. HLA-B*27, also associated with slow progression, only binds peptides that carry an arginine at position 2 (Marsh *et al.*, 2000).

A third line of evidence suggesting the importance of CTL in control of HIV infection is the demonstration that the selection of particular CTL escape mutations can precipitate loss of immune control (Barouch *et al.*, 2002; Feeney *et al.*, 2004; Goulder *et al.*, 1997). Taken together, and as discussed further below, these studies indicate the strong causal link connecting particular HLA molecules and the resulting CTL responses with effective control of HIV replication.

1.3. DISEASE OUTCOME MEDIATED BY CTL

1.3.1. Effective CTL responses and dominant role of HLA-B

The association between HIV immune control and expression of certain HLA class I molecules is most striking for alleles located in the HLA-B locus. For example, HLA-B*27, HLA-B*57 and HLA-B*51 have been associated with successful control of HIV infection whereas HLA-B alleles such as HLA-B*5802 and HLA-B*3502 have been associated with rapid disease progression (Honeyborne *et al.*, 2007; Kiepiela *et al.*, 2004; Leslie *et al.*, 2006; O'Brien *et al.*, 2001). The HLA-B locus is the most polymorphic of the three major HLA class I loci, with 817 alleles described compared with 486 HLA-A alleles and 263 HLA-C alleles (IGTM/HLA database). Indeed, the HLA-B locus is the most polymorphic region in the entire human genome reflecting the fact that this is a site of exceptionally strong balancing selection (Belich *et al.*, 1992; Watkins *et al.*, 1992) and the vital role played by HLA-B in immune protection from pathogens whose control is dependent upon CTL.

The mechanism by which particular HLA-B alleles mediate viral control of HIV provides a crucial clue to understanding which CTL responses need to be induced by an effective HIV vaccine. Recent studies have suggested that a critical factor linking these protective HLA-B alleles is the fact that they all present epitopes from within the HIV Gag protein, whereas HLA alleles associated with a lack of immune control present no, or few, Gag epitopes (Matthews *et al.*, 2008). Indeed, several population studies of HIV infection have shown that an increased breadth of Gag-specific $CD8^+$ T-cell responses correlates with decreased viral load, irrespective of HLA type, while no correlation has been observed for non-Gag-specific responses (Edwards *et al.*, 2002; Geldmacher *et al.*, 2007; Honeyborne *et al.*, 2007; Kiepiela *et al.*, 2007; Klein *et al.*, 1995; Masemola *et al.*, 2004; Novitsky *et al.*, 2003; Riviere *et al.*, 1989, 1995, Zuniga *et al.*, 2006). Studies of immune control of SIV in several different macaque models also suggest a key role for Gag as an immune target (Goulder and Watkins, 2008). In short, a broad Gag-specific CTL response