Book Reviews

The Biology of Complex Organisms (ed. Eichmann, K.), pp. 104. Birkhauser, Basel, Switzerland, 2002. ISBN 3 7643 6979 5. CHF 112.
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The first part of this book consists of six lectures read at a Symposium to mark the 40th Anniversary of the Max-Plank-Institute of Immunology in Freiburg, Germany. Contributors are Lewis Wolpert (*Evolution of development*), Rudolf Jaenisch (*The cloning of mammals: what are the problems?*), Martin Raff (*Size control and timing in development*), Charles Janeway Jr. (*How the immune system protects the body from infection*), Jacques Miller (*Biological curiosities: what can we learn from them?*) and Philippe Kourilsky (*Quality control of immune self non-self discrimination*). Although these articles are meant for a general audience, their content is by no means trivial and I enjoyed (and learned from) all of them. I was particularly interested in Wolpert's chapter, in which he refers to Haeckel, his gastraea and blastaea and the theory of recapitulation. Wolpert argues that gastrulation is similar in all animals because the process does actually recapitulate an ancient ancestor.

The second part of the book contains three chapters describing the past and recent history of immunological research at the MPI. There are photographs, facts and anecdotes, brought together from a variety of sources, that otherwise would have been difficult to access. All in all, this volume is a fitting tribute to those MPI scientists who have made so many outstanding contributions to science.

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Macrocyclic lactones in Antiparasite Therapy (ed. Vercruyse, J. & Rew, R. S.), pp. 448. Commonwealth Agricultural Bureau International (CABI Publishing), UK, 2002. ISBN 0 85199 617 5. £ 75.00 (US$ 140.00)
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Discovered in 1976 and introduced commercially in 1981, ivermectin was the first macrocyclic lactone developed for use in animals, its introduction revolutionized antiparasite control and it has since become the biggest selling antiparasite drug world wide. For the first time, there was a single compound that was safe and effective against both the larval stages and adults of the major parasitic nematodes as well as larval and adult arthropods. Ivermectin showed unprecedented high efficacies (often up to 100%) at doses 10 to 100 times lower than existing anthelmintics, with a wide safety margin and, because of its lipophylicity ivermectin persisted in the body giving a prophylactic effect. Since 1981 several new macrocyclic lactones have been developed for the control of external and internal parasites in a wide range of hosts whilst, at the same time, the first cases of drug resistance have emerged.

Comprising 14 specialist chapters the book gives an overview of the chemistry, pharmacology, safety, efficacy, resistance mechanisms and environmental impact of macrocyclic lactones and summarises their use in the control of parasites in animals and man. Each chapter is written by experts in the relevant field and the first 5 chapters give a general account of macrocyclic lactones, whilst the following 8 cover the use of macrocyclic lactones in specific hosts. The final chapter addresses future developments.

The discovery of the original *Streptomyces avermitilis* strain, optimisation, chemical structures and the basic pharmacology of ivermectin and its relatives is covered in Chapter 1. The pharmokinetic profile of macrocyclic lactones is reviewed in Chapter 2 and the different factors which influence pharmokinetic behaviour and how these can be used to optimize performance are discussed. The macrocyclic lactones all share the same pharmacological target, principally the glutamate gated chloride channels. Since glutamate gated chloride channels are restricted to nematodes and arthropods, this accounts for their selectivity and lack of effect on tapeworms and flukes. However, macrocyclic lactones do affect other classes of ion channel and may have multiple sites of action.

The main route for the clearance of macrocyclic lactones from the body is via the bile and as much as 96% of the administered dose can finish up in the faeces. This, coupled with the slow breakdown of these compounds, has led to concerns about the environmental impact of macrocyclic lactones. Chapter 4 gives a balanced account of this contentious area and points to the complex interacting factors which can be involved.

Resistance to macrocyclic lactones, often accompanied by multi-drug resistance, is an increasingly serious problem. As might be expected with a drug that has multiple sites of action, resistance is polygenic. Work, reviewed in Chapter 5, using the model nematode *C. elegans* shows that there are over 20 genes that confer low level resistance to avermectin, whilst additional genes confer high level resistance. In parasitic nematodes resistance may involve changes in the P-glycoprotein pump, increase in the density of glutamate binding sites and changes in binding affinity.

The different treatment strategies used in various regional husbandry regimes for domestic livestock

(horses, cattle, sheep, goats and pigs) are summarized in Chapters 6–9. The specific formulations, doses and modes and timing of administration used in different agroclimatic zones are described as is the resulting efficacy against the major nematode and arthropod parasites of the various regions. Drug persistence, withdrawal times and effects on animal production are also covered. In addition there are chapters covering domesticated wild ruminants (camel, deer including reindeer, bison, buffalo. Alpaca, Llama) and pets (dog, cat, ferret, rodents, rabbits, birds, reptiles and amphibians).

Of the various macrocyclic lacones, only ivermectin is licensed for human use and has principally been employed in mass distribution campaigns against *Onchocerca*. However, the broad range of antiparasite activity of ivermectin, including against mites and lice suggests possible wider uses and this is discussed in the penultimate chapter.

The final chapter considers the future use of macrocyclic lactones. As a class these drugs are superior to all other groups of current anthelmintics, offering an unprecedented combination of a broad spectrum of activity with a high degree of safety together with persistence and high potency. However, cultural and political trends on the one hand, together with market forces and problems with drug resistance in some areas may limit the use of these compounds, whilst the increase in companion animals and a desire to control zoonoses may lead to an increase.

The book should be of interest to specialists in parasitology, pharmacology and human and veterinary medicine. It provides a comprehensive and detailed review of the field (the first for over 10 years) and will be a valuable reference source. If you have a ferret with ear mites or a Bison with worms, help is at hand!

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Lyme Borreliosis. Biology, Epidemiology and Control (ed. Gray, J. S., Kahl, O., Lane, R. S. & Stanek, G.), pp. 347. International (CABI Publishing), UK, 2002. ISBN 0 85199 632 9. £75.
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Mention Lyme disease in polite society, and one is met by two contrasting responses. 'Lay' acquaintances, including academics from the Arts, jump with interest because they have very often had direct experience of infection, if not personally then *via* a friend or relation. Their interest is entirely justified as Lyme disease, or more correctly Lyme borreliosis, is the most common vector-borne infection throughout the northern temperate zones of the world. It circles the globe, from western to eastern Pacific shores, with gaps only in central USA. Recorded cases run to tens of thousands per year (Dennis & Hayes, ch. 10). Although not fatal, if the infection is not treated promptly with antibiotics, symptoms commonly progress from persistent fatigue, intense malaise and widespread pain to severe cutaneous, neurological, cardiac or arthritic disorders (Stanek *et al.*, ch. 1).

Biologist colleagues, on the other hand, habitually heave a sigh and declare the subject to be boring. Its clinical importance is seen, with some justification, as trivial besides the great killer vector-borne diseases of the tropics, and its vectors, ticks of the *Ixodes ricinus* complex of species, are amongst the least understood and most under-appreciated of all haematophages. Worse still, even today it is commonly but mistakenly perceived as a problem peculiar to the northeastern states of America. Its very name refers to the town, Lyme in Connecticut, where an unusual cluster of cases of childhood arthritis in 1975 sparked the eventual naming of parts of an ancient, but apparently (re-)emerging zoonosis. Those parts – ticks, genetically diverse spirochaete bacteria of the *Borrelia burgdorferi* complex, and a wide variety of vertebrate hosts such as rodents and birds to transmit the spirochaetes between ticks, and deer to feed the reproductive stage of ticks – are integrated into a whole whose dynamic complexity far out-strips the average insect-borne disease system. Therein lies its real interest. A quantitative explanation for the described epidemiology, within a single unified framework that encompasses the full geographical spectrum, poses an intellectual challenge sufficient to engage the best of both empirical and theoretical parasitologists.

Meanwhile, the paradoxical features of *B. burgdorferi s.l.* (Kurtenbach *et al.*, ch. 5) must surely capture the imagination of any microbiologist and focus the spotlight on questions for our post-genomic era. The majority of genes encoding proteins of the outer surface coat are hitherto unmatched in other organisms, and so-called 'virulence factors' identified for other pathogens have not been found. Pathological reactions are triggered out of all proportion to the few bacteria seen to reside in the vertebrate host, where they persist for long periods, even lifelong, despite strong stimulation of the adaptive immune system. The resulting high transmission potential enables this bacterial species complex to occupy a wide range of ecological conditions, while the diversity generated by 'localised sex' allows exploitation of distinct microenvironments at the species-specific tick-host interface.

It is now clear that the ubiquity of *B. burgdorferi s.l.*, alongside geographically and temporally variable patterns of infection and disease, is determined by interactions between the genetically and phenotypically diverse bacteria and an even more diverse

suite of hosts, mediated by ticks with their own inherent ecological variability. An understanding of this system requires a huge accumulation of facts in the first instance, many of which must come from conventional field work and transmission experiments to reveal the basic ecology of this zoonosis (Eisen & Lane, ch. 4; Gern & Humair, ch. 6; Korenberg *et al.*, ch. 7; Miyamoto & Masuzawa, ch. 8; Piesman, ch. 9). At the same time, we have seen two decades of fast-moving discoveries aided by new tools and techniques – from molecular genetics (Bergström *et al.*, ch. 3) to the use of satellite imagery (Stafford & Kitron, ch. 12) – that would not have been available had Lyme borreliosis 'arrived' any earlier. Within 13 years of its definitive identification in 1984, the genome of *B. burgdorferi s.l.* was published. The hope, of course, is that this will drive forward the search for new prophylactic and diagnostic devices. The first vaccine in the USA, surely one of the fastest to reach the general public, has already been withdrawn after adverse publicity (Hayes & Schriefer, ch. 11).

This explosion of truly multi-disciplinary information is gathered into this book. As well as adding to our specific *knowledge* of Lyme borreliosis, parts of this book also push back the frontiers of our general *understanding* of the biology of microbes and their transmission systems. And the book is nothing if not well referenced. Indeed, perhaps a little editorial pruning would not have come amiss here – no less than 100 out of the total 347 pages are devoted to bibliographies, with many citations repeated at the end of several, up to 4 or 5 chapters. This is offset by an extraordinary lack of figures. Epidemiology is essentially a quantitative discipline, and many a thousand words could have been replaced by a single well-designed figure. Out of a disappointing 36 figures in the whole book, only 7 are quantitative.

Despite these editorial shortcomings, the impressive array of science and scientists displayed in this book deserves to break down the curious asymmetry – the significant interest of, but the limited general professional interest in, *B. burgdorferi s.l.* Although it is primarily a book for people seeking specific information, it is also a rich source of ideas for research agendas for a wide range of specialists, from wildlife ecologists to bioinformaticists.

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