HLA and MHC: Genes, Molecules and Function. Edited by M. BROWNING and A. MCMICHAEL. Bios Scientific Publishers 1996. xvii+438 pages. Hard cover. Price £75. ISBN 1 85996 115 0.

This book provides a thorough review of just about every aspect of the human leucocyte antigen/major histocompatibility complex (HLA/MHC) from the evolution of MHC genes, their structure, polymorphisms and population genetics, to their cell biology, function and role in immunity and immunopathology. The book contains a wealth of factual information (everything you always wanted to know about the MHC but never dared to ask), including a bang up to date map of the whole region (Trowsdale, Chapter 2). However, the real strength of this book is the way it deals with the more speculative aspects of the subject, with different authors addressing the same subject from different viewpoints. In the case of HLA/MHC, much of the speculation revolves around explanations for the very high levels of allelic polymorphism, the population structure of HLA alleles and the presence of such strong linkage disequilibrium.

For classical geneticists the MHC is the example, *par excellence*, of allelic diversity, but explaining the factors leading to and maintaining this diversity has been a source of intense and often acrimonious debate. This topic is touched upon in almost every chapter of the book. Far from being boringly repetitive, however, it is fascinating to observe the differences in opinions, and the evidence cited in support or refutation of the various theories by evolutionists, population geneticists, immunologists and clinicians. Jim Kaufman (Chapter 1), in particular, treads carefully through this minefield putting HLA into an evolutionary context, explaining the possible alternatives to immune selection as the driving force behind the polymorphism and explaining how the various theories can be reconciled. In contrast, Wells and Parham (Chapter 2) come down much more clearly on the side of immune selection as the major force behind the generation and maintenance of polymorphism whilst noting that there are marked differences between the class I HLA-A and HLA-B loci in the pattern of sequence divergence within allelic lineages. HLA-A shows strong evidence of heterosis (heterozygote advantage) but this is much less obvious in HLA-B where the pattern is more consistent with frequency-dependent selection due to frequent exposure to new pathogens.

In similar vein, Apple and Erlich (Chapter 5) deduce that the selective forces acting on different class II loci may vary as the distribution of *DPB1* alleles within populations differs from that of *DRB1*, *DQA1* and *DQB1* alleles. For the *DR* and *DQ* loci there is a relatively even frequency of the various alleles within the population, with no one allele predominating (suggesting balancing selection) but in most populations a single *DPB1* allele will tend to predominate (frequencies of 35–40%) with the other alleles present at low frequency (suggestive of neutrality). It is unlikely however that *DPB1* is selectively neutral as allelic variation is still concentrated in codons for amino acid residues around the peptide binding groove and nonsynonymous substitutions greatly outnumber synonymous ones. Apple and Erlich also point out that the strong linkage disequilibrium within the MHC, including some extended haplotypes including both class I and class II loci, provides strong evidence of selection for particular haplotype combinations which cannot be explained simply on the basis of preferential pairing of the α and β chains of HLA heterodimers.

Although the distribution of alleles within a population can be used to make educated guesses about evolutionary forces, several authors point out that the diversity within discrete populations is generally much less than within the species as a whole – suggesting that estimates of the importance of pathogen-driven frequency-dependent selection may be overgenerous. Indeed Kaufman claims that '...all *Mhc* haplotypes are more or less resistant [to any infectious pathogen], with large numbers of patients and careful statistics needed to see any difference [in susceptibility'].

The generation of diversity within the Class II system is discussed by Apple and Erlich (Chapter 5) who cite recent data relating to the rate of inter-allelic gene conversion within *HLA-DPB1* in the human germline (sperm) (Zangenberg *et al.*, 1995, *Nature Genetics* **10**: 407–414) which suggests that the mutation rate is 1 to 3 orders of magnitude higher than expected for a 300 bp segment. Whilst this might indicate that gene conversion leads to particularly rapid generation of diversity in this region of the genome, few comparable data are yet available for other loci and estimates of mutation rate in sperm are bound to be higher than estimates for the organism as a whole. The authors, however, conclude that rapid diversification of Class II is due to a combination of both high rates of germ line diversification and strong selective forces.

Another area of controversy in the MHC is the explanation for strong HLA associations with autoimmune diseases (Chapters 15 and 16). The simple explanations, that certain HLA molecules bind and present to the immune system certain self-peptides that are not presented by other HLA molecules, is challenged by recent data cited by Wassmuth (Chapter 8). Polymorphisms within the promoter region of *DQA1* (rather than the expressed sequence of any particular *DQA1* allele) are highly associated with the autoimmune disease, juvenile chronic arthritis (Haas *et al.*, 1995, *Tissue Antigens* **45**: 317–321) demonstrating that factors other than the peptide-binding specificity of the protein are involved. Promoter variability may be associated with differences in

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transcription leading, for example, to changes in the stoichiometry – and thus levels of cell surface expression – of class II heterodimers. Similarly, in rats transgenic for the class I *HLA-B27*, the development of spondylarthropathies correlates with the levels of expression of the transgene (cited by Hall and Bowness, Chapter 15). Wassmuth (Chapter 8) also refers to the role of class II transcription factor mutations in the aetiology of a group of congenital immunodeficiencies, where there is a complete failure to express certain HLA loci with subsequent failure of lymphocyte selection and maturation in the thymus.

In addition to chapters on MHC assembly and transport, crystal structure and function in antigen presentation, the book also contains an excellent chapter on serological and molecular methods for HLA typing (Chapter 6), a summary of the levels of constitutive HLA antigen expression on different tissues and cell types (Chapters 7 and 8) and a useful compilation of the various peptide binding motifs for different class I and class II alleles (Chapter 12). Finally, the description of the gene hunting exercise for HLA class III genes (Chapter 3) is a fine example of the new approaches to genome analysis. This chapter also gives an insight into the problems of transcriptional regulation of closely spaced genes – genes-within-genes are a feature of the class III region.

On the whole, the book is well edited and acceptably up to date (most chapters contain a liberal scattering of 1995 references and there are occasional 1996 citations). Anyone reading the book from cover to cover will find extensive repetition of the basic concepts of the MHC, but the book is not really designed to be read in this way. Each chapter is self contained and intelligible without reference to others (although there are a number of abbreviations which are not explained either in the text or in the abbreviations list at the front of the book). Having said that, reading the book in its entirety is very informative as it is only then that the differences in nuance become apparent.

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The Shape of Life – Genes, Development and Evolution of Animal Forms, by RUDOLF A. RAFF. University of Chicago Press 1996. 544 pages. ISBN 0 226 70265 0 (cloth), 0-226-70266-9 (paper). Price £43.95 ($55) cloth, £23.95 ($29.95) paper.

There has been remarkable progress in our understanding of how genes control development and this opens up quite new ways of thinking about evolution. For all evolutionary changes in multicellular animals and plans are due to changes in their DNA changing how the organisms develops. So while it is possible to have an evolutionary theory without any consideration of embryonic development, such a theory will always be deficient. One of the key questions, for example, is why out of the millions of animal species there are so few body plans – thirty-five. The answer must involve a contribution from development. Again, if one wishes to understand how limbs developed from fins, one needs to know how the limb and fin develop and how the genes control these processes. These are central themes of this book.

Raff makes clear that homology is the basis for all evolutionary comparison. Unfortunately, it is a concept fraught with difficulties. How does one decide if the insect leg is homologous or analogous to the vertebrate limb? Structures, it is claimed that are clearly homologous, do not always arise in the same way in development. If that is true then one cannot use the most intuitively satisfactory definition, namely homologous structures have a similar developmental programme together with evolutionary continuity.

An examination of metazoan origin suggests that just before the visible Cambrian radiation 'the pace of metazoan evolution seems to have quickened. It is likely that the truly defining steps in metazoan evolution occurred during that interval'. How wonderful it would be to understand just what happened then!

There is an analysis of phylogenies from molecular and morphological approaches which have yet to be reconciled, together with cladistic and evolutionary classification. One needs to be able to identify primitive from derived states. There is also the problem of proper dating of the fossil record which, if incorrect, can lead to errors in calibrating molecular clocks.

One of the most exciting discoveries has been that the same set of genes – the *Hox* genes – are involved in providing positional identity to cells along the antero-posterior axis of many animals. This pattern of gene activity is characteristic of the phylotypic stage – the stage at which the body plan of a phylum is blocked out. However, both before and after this stage there can be considerable variation. Just why this stage is so well conserved is a matter of much discussion. It may be just too difficult to alter once it has been established. My own view is that this is when the basic pattern of positional identities is established and then the positional information can be interpreted in many different ways. To change this basic co-ordinate system would involve a major leap and would be unnecessary.

Whatever the reason, conservation of body plans provides a developmental constraint. Developmental constraints are important for understanding evolution for they determine what sorts of animal forms can evolve. It is difficult to imagine mice developing feathers as just too many changes in the developmental programme are required and each has to be adaptive.

Raff thinks that changes in timing of developmental events – heterochrony – has been the single most pervasive idea in evolutionary developmental biology. But he makes a critical assessment as to whether such