Book Reviews

Horse Genetics. By ANN T. BOWLING. CAB International, 1996. 200 + xvii pages. Price £19.95, $35.00. ISBN 0 85199 101 7.

This book is intended to provide an overview of basic genetic principles that are illustrated using examples of horse genes and horse breeding. The first chapter is a brief summary of the structure of genes and chromosomes, and of Mendelian transmission genetics. The next eight chapters, covering fully one-third of the book, is an extensive description of the alleles of major loci that cause variation in coat colour, and their interactions. These are followed by separate chapters on parentage testing of horses, medical genetics, the horse karyotype and chromosomal abnormalities, genetics of performance traits, pedigrees and breeding schemes, genetic versus environmental and sire versus dam factors affecting development, genetic descriptions of breeds, the horse gene map, and a brief overview of the genus *Equus*. The penultimate chapter is a compilation of common questions about horse genetics and their answers, and the book ends with a look to the future of horse genetics.

This book is not a general genetics text. Horse genetics is in the dark ages relative to model organisms like yeast, *C. elegans*, *Drosophila* and mice, and even relative to other domesticated animals like cattle, sheep and poultry. To illustrate, horses have 32 chromosomes, but only six autosomal linkage groups have been described! Thus it is not possible to write a textbook of modern genetics using solely equine examples, and the breadth of genetic principles addressed here is correspondingly highly restricted to chromosomal mechanics and single gene segregation in pedigrees and populations. Neither is this book a monograph of horse genetics; the level is too introductory in many places, there is much redundancy, and quantitative genetics is barely discussed. Rather, this book is a hybrid between an exposition of the first principles of transmission genetics and a summary of the current state of knowledge of horse genetics, and as such is unlikely to be adopted as a reference in college-level courses or studied by professional horse breeders.

For whom, then, is this book intended? In the United States and Britain, horse breeding is in the hands of individual mare and stallion owners, who decide what mares to breed, what stallions to use, and are responsible for registering the foal. For these individual breeders *Horse Genetics* should be a treasure trove of useful information. Most of the topics covered are of immediate practical interest, and the weight given to the topics reflects both what is known and what is deemed important. Predicting what the coat colour of the offspring of a particular mating will be goes beyond curiosity for many breeders of animals whose registration and consequent value depends on the expression of the correct colour pattern (for example, American Paint Horses, Palominos and Appaloosas). The chapters on the genetics of coat colour are the clearest description of this subject I have read to date. The repetition of the same information (and in one case, even the same figure) between chapters is a consequence of an effort to make each chapter a module that stands on its own, if a reader is specifically interested in only one colour pattern. Most breed societies require parentage testing of foals for registration, so the description of the diagnostic polymorphic blood group, electrophoretic and DNA markers used and the principles of sire (or dam) exclusion are of intrinsic interest. Also useful is the discussion of common genetic and cytological defects. For the most part, the treatment of these subjects is self-contained within the pages of the volume, but occasional technical terms appear without sufficient definition. For example, it is doubtful whether the concept of heritability has been adequately explained to the intended readers, although all that is said is accurate.

Modern horse sports (dressage, driving, eventing, stadium jumping, polo and racing) require superb equine athletes. Each sport emphasizes different physical attributes, but all place a high premium on physical and temperamental soundness. The best advice one could offer an individual breeder is to breed only the best mares to the best stallions, where best is defined by objective performance criteria. A breeder reading this book could get the impression that the only use of genetics is to predict coat colour. Nowhere are the principles of artificial selection, so successful in producing performance horses such as the Thoroughbred race horse and various European Warmblood sport horse breeds, discussed.

Performance testing and progeny testing are long accepted animal breeding practices that are rigorously applied for European breeds, where breeding decisions are not made by individual owners. Stallion candidates are evaluated at a young age on their own performance by a panel of medical experts and trainers. Only the progeny of the best are eligible for registration; further, a stallion can be disapproved should his progeny not themselves perform well. These practices are no doubt the reason these breeds dominate the current market. Yet the discussion of whom to breed to whom is mostly concerned with inbreeding. Inbreeding beyond a certain level (usually first cousins) is generally prohibited by performance horse breed societies, for the obvious reason that inbreeding increases homozygosity, and homozygosity of deleterious recessive genes leads to a decline in viability, fertility and performance (inbreeding depression). Close inbreeding and linebreeding to exceptional ancestors is common in some American breeds, and has led to an increase in frequency of individuals physically and temperamentally not suited for modern competition. One would have thought that these principles could have been more clearly elucidated. Instead, the concept of inbreeding as a mechanism for maintaining genetic diversity if there are sufficient inbred lines is promoted. While true for selectively neutral genes, this concept does not work well as a breeding strategy because of the inbreeding depression within lines, and should be actively discouraged.

Horse Genetics fills an important niche – providing accurate genetic information to the many individual breeders of tomorrow's equine athletes and family pets. I hope that the next edition will add an introduction to the principles and application to horses of artificial selection to the already excellent coverage of Mendelian traits.

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Epigenetic Mechanisms of Gene Regulation. Edited by V. E. A. Russo, R. A. Martienssen and A. D. Riggs. Cold Spring Harbor Laboratory Press, 1996. 693 + xii pages. Price $125. ISBN 0 87969 490 4.

C. H. Waddington, whose name does not appear in the index of this book, invented the term epigenetic to describe the complex of largely unknown interactions, acting at a level transcending that of the constant individual genes, that steer organisms into their various channels of development. Today epigenetics, meaning clonal transmission of alternative cell states without variation in the underlying DNA sequence, is perhaps the most important new frontier of cell biology. This typically authoritative volume from Cold Spring Harbor, comprising 37 review articles and three reprints of historic papers, sets the current scene.

Apart from one article by Grandjean *et al*. on gene silencing in diploid cells of *Bacillus subtilis* (reminding us of the earlier work on this topic by Rollin Hotchkiss) all the systems described are in eukaryotes. They fall into two rather distinct categories: firstly, epigenetic changes, mostly involving gene silencing, that are regularly programmed in normal life cycles; secondly, unscheduled silencing brought on by genetic accident or experimental manipulation – most often by the introduction of supernumerary or exotic gene copies. The first category includes mammalian imprinting (Surani and Reik and their respective colleagues) and female X−inactivation (Riggs and Porter, Avner), the roles of the *Polycomb* (*Pc*)-group and *trithorax* (*trx*)-group protein complexes in stabilizing states of gene inactivity or activity in *Drosophila* (Paro and Harte, Pirrotta), and the silencing of the stand-by yeast mating type loci (Holmes *et al*. on *Saccharomyces* and Allshire on *Sch. pombe*).

Most of the examples of unscheduled epigenetic change come from flowering plants, with a few from fungi. Most concern plant pigmentation rather than gross morphology, but one suspects that several old plant problems now almost lost in the mists of time – rogue peas and so on – may belong in the same broad category. Matzke and Matzke bring on board the long-standing anomaly of somaclonal variation – heritable differences arising among vegetative clones of the same plant. The difference, described by Meins *et al*., between tobacco explants with regard to cytokinin requirement could also be called somaclonal, though here there is a hint of a link to a programmed change in potential during plant development.

The big question about epigenetic states, of course, is how they are perpetuated through cycles of cell division. The first, and still by far the neatest answer was provided in 1975 by Holliday and Pugh who pointed out that a DNA methylase that acted on half-methylated DNA could maintain specific states of methylation through cycles of DNA replication. Holliday, in the first article after the introduction, still holds to the view that methylation is the key to epigenetics. Indeed the evidence cited in the following article by Holliday and others, to the effect that gene silencing in mammalian cell cultures can be provoked by 5-methyl deoxycytidine, as well as reversed by 5-azacytidine, is persuasive. Methylation has indeed been shown to accompany gene silencing in most of the mammalian, plant and filamentous fungal examples. The trouble is that *Drosophila* and yeast do not have detectable methylation of their DNA and so we cannot make it an essential part of a general model. Riggs and Porter, in their introductory overview, remind us that self-perpetuating cell states do not necessarily have to be explained in terms of chromosome structure, and cite two classic examples from prokaryotes of epigenetic mechanisms that seemingly operate just with naked DNA and gene-specific regulators: the self-maintenance of the activity of the

E. coli lac operon (permease brings in lactose to induce more permease) and the stabilization of lambda lysogeny (the repressor of the lytic pathway promotes the transcription of its own messenger). Meins inclines to similar kinds of model for eukaryotes. But on the whole opinion seems to be tending to the view that epigenetic switches, at least in eukaryotes, are attributable to self-perpetuating changes in chromatin, a chameleon-like substance the epigenetic potential of which is discussed in the article by Kass and Wolffe. Even without DNA methylation, chromatin has plenty of scope for variation, with numerous 'optional' proteins forming mutually exclusive activating or silencing complexes, and even the ever-present histones subject to positional changes and different levels of acetylation. Among other possibilities for self-perpetuation, Kass and Wolffe suggest that a multimeric transcriptional complex, divided between daughter DNA strands at S-phase, could nucleate reassembly of the same complex on each daughter chromatid. Essentially the same idea could apply to the perpetuation of multimeric repressing complexes, with perhaps additional stability conferred by DNA methylation, which is likely to be self-maintaining in its own right.

The concept of open-ended self-seeding chromatin complexes may help to explain the transmission of states of gene activity not only through cycles of replication but also along chromosomes, as in *Drosophila* position effect variegation (*oozing*, as Henikoff calls it in his article), and even in *trans* between homologues, as in maize paramutation (articles by Kermicle and Chandler *et al.*). In this connection it was disappointing to have no article on the MIP phenomenon in the fungus *Ascobolus immersus*, in which there is heritable but reversible silencing of duplicated genes in premeiotic haploid cells. Results recently published in *Cell* by Rossignol and Colot imply that the MIP'd condition, once established, is contagious between alleles engaged in meiotic recombination. RIP, the related *Neurospora* phenomenon, is dealt with in an article by its discoverer Selker; this is a more complicated system with both methylation and numerous base-pair transitions, standing outside the epigenetic mainstream (if there is one).

This publication is a milestone, but there are clearly many miles still to go. I hope that the next such volume will tell us more about the nature of the signals that provoke epigenetic changes as well as about their modes of propagation once established. And one would like to see more connections made between programmed and unscheduled epigenetic phenomena. Is there underlying unity here? Barbara McClintock, to whose memory this volume is dedicated, would have expected so.

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Gene Therapy. Edited by N. R. Lemoine and D. N. Cooper. Bios Scientific Publishers, 1996. 343 + xiv pages. Price £60, hard cover. ISBN 1 859962 05 X.

Gene Therapy Protocols. Edited by Paul D. Robbins. Humana Press, 1997. 432 + xiv pages. Price $74.50 ISBN 0 89603 307 4.

It is fair to say that in recent years research endeavour in the field of gene therapy has received excessive attention from both the scientific press and the lay media. Initially there was over-optimistic hype and subsequent attention was inappropriately negative. Latterly there has been relative media calm and it now seems reasonable to expect that progress can be made and acknowledged in the literature at a rate that is more in keeping with scientific reality. There are now a large number of clinical trials in progress that are applying gene therapy to multifactorial diseases such as cancer and cardiovascular disease, as well as to heritable single gene disorders and other less well defined but important clinical diseases. Areas where gene therapy may first show real clinical advances include cystic fibrosis, where it may be possible to ameliorate the damage caused to affected lungs. Cancer gene therapy, most probably in combination with conventional treatments, also holds much promise. While it is unlikely that many cures will spring directly from these trials, enough will be learned about *in vivo* gene therapy to allow progress analogous to that seen in Phase I and II trials of conventional chemotherapeutic agents. Now that the media limelight has dimmed and the pressure to produce dramatic results has abated, we can hope for some rational progress. In this context, the two books that are the subject of this review are timely and valuable in their different ways.

Lemoine and Cooper's volume comprises 18 chapters of two general types. The first ten are concerned with technological aspects of gene therapy including vectoring systems, the use of animal models and gene targeting. Chapters 11 to 18 comprise reviews on the application of gene therapy strategies to various diseases including cystic fibrosis, haemophilia, adenosine deaminase deficiency, cardiovascular disease, cancer gene therapy, muscular dystrophy and neurological disease. Each chapter is written by a leader in the field reviewed. A foreword by Bob Williamson takes a pragmatic view of the place of gene therapy in the treatment of disease. Karol Sikora, in chapter 1, follows with a discussion of suitable target diseases, and ethical and safety considerations; he also makes brief reference to the application to each of the specific diseases which are dealt with in greater detail later in the volume. This chapter gives an overview of the scope and also the limitations of gene therapy applied to human disease. Sikora points out the many problems to be solved for the application of gene therapy in clinical practice, but overall his contribution reflects the optimism of the book in general.

The initial chapters provide an excellent review of potential physical methods of targeting gene transfer in addition to receptor-mediated gene delivery with some reference to tissue-specific expression of the transgene. The chapters on retroviral, adenoviral, adeno-associated viral delivery systems in addition to liposome-mediated gene transfer are all excellent, written by major figures in their respective fields. The chapter on the role of animal models in gene therapy gives a review of different strategies in the use of animal models in general but with particular reference to their use as targets for corrective gene therapy or for rescue experiments. The authors point out the major importance of modifiers of monogenic human diseases; it is only in studying whole animals that some of these complications can be addressed.

The second portion of the book addresses specific conditions where gene therapy is being actively applied. The prime example is cystic fibrosis where there are several trials world-wide using a variety of different vectoring systems for gene replacement therapy, and here the chapter by Caplan and Alton is very informative. Two whole chapters are devoted to the application of gene therapy to various forms of cancer, the first dealing with genetic intervention and the second with immune modulation using transduction of co-stimulatory molecules, cytokines or DNA vaccination.

Overall, the book is extremely well written and well documented and gives a balanced view of a complex area of scientific endeavour. It is aimed at postgraduate students and scientists with a general interest in the potential applications of gene therapy. I would see the book as a useful addition to the private book collections of researchers and clinicians as well as to the libraries of genetic and therapeutic institutions. There is little to criticize in either the content or the style of the presentation.

Lemoine and Cooper do not set out to provide a how-to-do-it manual. This is more the role of Paul Robbins' book, which comes in a plastic ringed spine format, signifying its intended use as a practical laboratory manual. As such it succeeds admirably, providing detailed methods for working with gene transfer techniques. The first of its two parts addresses the use of specific vectoring systems for gene transfer, while the second concerns the application of gene transfer to specific tissues such as a broncho-alveolar tree, liver and cancer to name a few. The authorship is impressive, including as it does a number of international leaders in their respective areas of interest. Each of the authors has provided a brief résumé of general principles followed by a detailed description of methods employed. The detail is to the level of providing concentrations of various constituents of culture medium of various transfer solutions and of the actual methodology of growing cells, transducing cells, production of adenovirus or retroviral vectors, to name but a few of the applications that are discussed Every chapter is well referenced, though some chapters may have more extensive bibliography than others.

Overall the book succeeds in its aim to be a useful manual, either in the laboratory or on the library shelf of institutes using gene transfer relatively infrequently. Institutions involved in gene therapy will usually have such detailed protocol descriptions developed 'in-house', but it is still valuable to compare alternative methodologies, and the tips and nuances provided in every chapter will often be helpful.

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