

Book Reviews

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Zebrafish: A Practical Approach. Edited by C. NÜSSEIN-VOLHARD and R. DAHM. Oxford University Press. 2002. 322 pages. ISBN 0 19 963808 X. Price £40.00 (paperback). ISBN 0 19 963809 8. Price £80.00 (hardback).

Use of the zebrafish as a model organism for laboratory research has transformed our understanding of the molecular and cellular mechanisms underlying vertebrate development. This book impressively describes how to combine classical genetic analysis in this organism with techniques for molecular analysis of gene function and experimental manipulation of embryos, in a way that is sure to inspire an expanding community of scientists to exploit the zebrafish system in their research. Zebrafish embryos are optically clear and develop rapidly. Moreover, the generation time of this tropical fish is short and adults can be maintained at high density in laboratory aquaria. These features, together with the fact that germ cells can be efficiently mutagenized using either chemical or retroviral mutagens, make zebrafish particularly amenable to large-scale forward genetic screens. Phage geneticist George Streisinger and his colleagues first exploited the advantages of working with this organism and established techniques for laboratory research using zebrafish during the 1970s and 1980s. In the early 1990s, C. Nüsslein-Volhard and W. Driever vastly expanded the scope of studies with this organism when their groups pioneered large-scale, systematic genetic screens that yielded mutant collections of an astonishing depth, breadth and quality, giving myriad insights into the genetic control of developmental processes. This book now builds on the methodological principles established by these groundbreaking investigations to provide a comprehensive, up-to-date manual for laboratory work with zebrafish.

The book comprises an introduction, together with seven main technical chapters and three appendices. This organisation is logical, useful and further augmented by an extensive Index. Chapter topics include how to set up a zebrafish facility, how to stock it with interesting strains and maintain them, and then how to analyse mutant phenotypes and genotypes, clone

genes and design genetic screens to identify novel mutations. Each chapter has been written by one or more zebrafish researchers with particular expertise in the topic under review, and each contains many neatly formatted protocols that make the book very easy to use at the bench. The uniformly lucid text is richly illustrated throughout with high quality black and white photographs and line drawings that add valuable information, and a collection of colour plates is also provided to illustrate key technical points or to provide interpretable examples of experimental results. Whilst the power of classical genetic analysis in zebrafish is a dominant theme reinforced by many of the chapters in this book, I particularly enjoyed Chapter 4 by Kane and Kishimoto, which elegantly explains how to exploit zebrafish for lineage tracing and other studies of cell fate using modern experimental embryological techniques. Such experiments are frequently required for gene function analysis *in vivo* and the authors explain how they can best be tackled in zebrafish. Another fascinating section of the book is Chapter 5 by Gilmour, Jessen and Lin, which explains how to experimentally manipulate gene expression using knock-down approaches with modified oligonucleotides, transient gain-of-function experiments with microinjected mRNAs and plasmids, as well as stable transgenesis using small plasmid and modified BAC clones.

The appendices include an extremely useful and beautifully illustrated atlas of embryonic development, and a Table that summarizes the characteristics of more than 700 known mutations. As more than 80% of these mutated genes still remain to be cloned, future studies with these mutants promise to yield many fascinating new insights into the molecular and cellular mechanisms that regulate embryonic development. Although this book will find its greatest following in the developmental biology community, it is likely to enjoy an ever-widening readership in the coming years, as the vast potential of zebrafish for dissecting physiological functions and understanding human disease processes is realised.

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Reshaping Life: Key Issues in Genetic Engineering.
G. J. V. NOSSAL and R. L. COPPEL. Cambridge University Press. 2002. 253 pages. ISBN 0 521 52423 7. Price £16.95 (paperback). ISBN 0 521 81878 8. Price £45.00 (hardback).

It is evident that the interface between science and society is going to keep changing indefinitely. History has not come to an end, contrary to a widely-disseminated view of the historian Francis Fukuyama, and even he has recanted. His main reason for changing his mind was apparently the realization that the advance of science and technology would continue to affect society in unpredicted ways, with great political repercussions. This cuts both ways: the attitudes of society towards science, and consequent actions, are equally likely to be unpredictable and subject to chance. Genetics is a prominent, even notorious, area of science in this respect. There is a huge amount of current interest in genetics-based technologies, and correspondingly huge amounts of hype and scaremongering. Much would be gained if the public had a better appreciation of the techniques and issues involved. Books such as this, which is intended for the intelligent non-scientist in need of education on the basics of genetic manipulation and its consequences for society, are therefore very welcome.

So, if you knew nothing at all about genetic engineering, would this be a good place to start? The short answer is yes, assuming a reasonable level of intelligence and persistence on the part of the reader. The book starts with a clear but probably too detailed account of cellular and molecular biology and of genetic manipulation techniques. Non-scientific readers are encouraged to skip Chapters two and three, which deal with some of the actual methods on which genetic engineering depends. The fourth chapter deals with genomes, at a somewhat less technical level, and discusses the benefits to be derived from complete genome sequence information, both from the human genome and from other significant organisms such as pathogens. The treatment here is a bit thin; for example, the authors do not seem to realize the importance of comparative genomics.

The major emphasis of the book is on medical applications, and the impact of genetic engineering on both diagnosis and treatment. Two chapters deal with recombinant DNA technology for expressing hormones and growth factors, and with genes as diagnostic probes, both for the analysis and detection of genetic diseases, and also for applications such as forensic DNA fingerprinting and palaeobiology. Vaccines and vaccine development are dealt with at some length, both in terms of those already produced by the biotechnology industry, and in terms of future possible developments.

The impact of new technologies on drug discovery and development gets less attention than it deserves, and the word pharmacogenomics does not appear (well, maybe that is not so regrettable).

A separate chapter is devoted to gene therapy, cellular engineering and mammalian cloning, with the usual comments about the futility of human cloning for the purposes of imagined immortality. As the authors remark, however, one can certainly imagine scenarios where human cloning would provide a means of assuaging grief, without any great ethical problems. They are suitably realistic as to the likelihood of human cloning being achieved sooner or later, in some form or another, despite the extreme inefficiency and risk that such experiments would entail.

Another section discusses genetically manipulated organisms, covering both low-profile applications such as the use of bacteria in mining and bioremediation, and the much more controversial subject of GM agriculture. These issues, and descriptions of the biotechnology industry, take the authors on to wider considerations of scientific ethics and public policy.

This is the third edition of a book originally written by the eminent immunologist Gustav Nossal, and now re-written with Ross Coppel, another distinguished Australian biologist, as co-author. The first edition of 'Reshaping Life' was published in 1984, and to some extent age is beginning to tell. For any work of this type, there comes a time to start over again from scratch, rather than to update and modify in successive editions. Consequently, the initial chapters dealing with genetic engineering techniques go into unnecessary detail on some methods, such as library screening with degenerate probes, which are already beginning to fade into scientific history, and it would not greatly benefit a non-scientific reader to know about them. Conversely, there is no mention or explanation of PCR until halfway through the book, although this technique has become central to modern molecular genetics and is also easily understood by lay people. One of the most important aspects of genetic engineering is the sheer ingenuity of so many of the methods being invented and developed, and the book could have conveyed a better sense of the excitement of working in contemporary genetics, either in industry or in academia. PCR and its myriad applications provide a wonderful example.

Nevertheless, the coverage of key issues that already have public impact, or are likely to do so in the future, is good. The authors maintain a reasonable balance between the undeniable success stories (such as mass-scale production of erythropoietin and other hormones) and the technologies that have yet to fulfill their promise (such as gene therapy).

In a few places, especially towards the end, the book gets bogged down in issues of local Australian science politics, but for the most part it retains the

necessary international perspective. Attitudes towards genetic manipulation differ enormously from country to country, to the initial bafflement of many scientists. Here, as in other contentious areas of technology, it is not just the public that needs educating about science, it is also the scientists that need educating about politics, law and business. Scientists from different countries usually communicate easily and happily with each other, because they have similar backgrounds, training and outlook, so the real differences in public attitudes to science around the world, arising from different political systems and cultures, tend to come as a nasty surprise.

The authors also spend some time discussing biotechnology and the associated proliferation of start-up companies, in a more optimistic vein than the current state of the biotech market would justify. They do not make the point that most biotech start-ups seem to perish from the absence of a sound business plan, not from lack of scientific ideas or enthusiasm.

In keeping with the generally cautious, balanced treatment provided in this book, the final chapter, dealing with 'Distant horizons', contains no remarkable visions or predictions. Not for these authors the cheerful contemplation of possible gene-dominated futures, as laid out in books such as Lee Silver's 'Re-making Eden', only a few straightforward extrapolations and speculations. Unlike Silver, however, it is not the authors' intention to provoke, only to explain and discuss, and in this they are largely successful. Overall, the book is clear, readable and worthy.

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Ageless Quest: One Scientist's Search for Genes that Prolong Youth. L. GUARENTE. Cold Spring Harbor Laboratory Press. 2003. 154 pages. ISBN 0 87969 652 4. Price £14 (hardback).

This is an unusual book; it is rare for a practising scientist in mid-career to provide an autobiographical account of his work for a general audience. Lenny Guarente gives an uninhibited portrayal of the important discoveries of his laboratory concerning some genetic and molecular processes that control lifespan. The science is interspersed with personal reminiscences, especially about his upbringing as a son of a lower middle-class Italian-American family. Guarente is also remarkably frank about the personalities of the various graduate students and post-docs who contributed to the work (I am not sure how they will feel about this). He also emphasises the intensely competitive atmosphere of top-rank research in molecular

genetics, at least in the USA, which makes me feel relieved that I work on population genetics.

The theme of the book is the tortuous path that led to the discovery of the role of the Sir2 gene as a key regulator of lifespan in both budding yeast and *Caenorhabditis elegans* (this gene had originally been identified as a member of a group of genes involved in silencing the mating type genes of yeast). Guarente gives a vivid account of the twists and turns that started with his initial interest in the phenomenon of 'ageing' in yeast, whose asymmetrical mode of cell division enables a clear distinction to be made between mother and daughter cells. After a number of divisions (around 20 under standard laboratory culture conditions), a mother cell loses its capacity to divide again, and soon dies (in the absence of sexual reproduction). The probability of survival of a cohort of newly-formed cells declines with age, with an increasing mortality rate per unit time as age increases, similarly to age-dependent mortality in multicellular organisms. There is therefore a real sense in which yeast cells senesce, despite yeast's lack of multicellularity. Guarente describes how his laboratory developed a method for screening yeast for mutations with increased lifespan, a method which has also been successfully applied to more conventional models of ageing such as *Drosophila melanogaster* and *C. elegans*. They concentrated their efforts on a mutation which turned out to be in the Sir4 gene involved in mating-type silencing, and showed that this mutation suppresses the accumulation of extra-chromosomal circles of ribosomal DNA, which Guarente believes is a key cause of senescence in yeast. This led to the discovery that loss-of-function mutations of Sir2 reduce life-span, whereas duplications of Sir2 enhance it, and suppress the formation of extrachromosomal circles of rDNA. Guarente's lab went on to show that Sir2 is an NAD-dependent histone deacetylase. In *C. elegans*, the homologue of Sir2 represses the insulin signalling pathway, which other workers had shown to reduce lifespan and dauer formation; duplications of Sir2 enhance lifespan. Guarente speculates that the evolutionary origin of this role of Sir2 is the need to respond to a reduction in resource availability in times of scarcity, slowing reproduction and ageing until things improve.

Guarente does a good job of portraying lab-based research, in a way that should be accessible to the intelligent non-biologist. The biology of ageing has become a prominent field, with some spectacular advances in our knowledge of insulin-like signalling pathways that regulate ageing in a variety of different eukaryotes, as well as a well-established evolutionary theory of ageing. These advances are described briefly but clearly by Guarente, whose book emphasises his own contributions. He is rightly circumspect on the question of whether a cure for ageing is round the

corner, but believes that ways of ameliorating some aspects of the ageing process will soon become available. One caveat that makes me less optimistic than Guarente about the prospects for applications of the discoveries he describes is that these do not tell us much about what is happening during the ageing process. The effect of downregulating the signalling pathways is to push deterioration back in time, not to prevent it. There is also the concern that interference with a normally operating system must have adverse effects on other functions and net fitness under normal conditions, otherwise they would not have been put in place by natural selection.

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Seeds of Concern: The genetic manipulation of plants.

D. R. MURRAY. CABI Publishing. 156 pages. ISBN 0 85199 725 2. Price £19.95 (paperback).

It is commonplace amongst groups of ‘concerned’ western, wealthy people to decry the present day, to predict apocalypse around the corner and to blame it all on technology. One of the battlefields on which such ideologues present their luddite views is in agriculture and in particular GM crops. Murray’s book ‘Seeds of Concern’ is another of these written with a superficial knowledge of plant molecular biology and contains a fairly predictable message.

The present apocalyptic movement started with Carson’s ‘Silent Spring’, a book written by a marine ecologist about toxicology, a subject about which she understood very little. But like many ‘convinced’ people lack of knowledge did not inhibit the offering of opinions and anecdotal evidence as support. Similarly Murray offers opinions mixed with selected facts on a subject of which he clearly has weak knowledge and no practical experience. As with Carson’s book there are plenty of errors and very obvious omissions: facts must not get in the way of the message.

A touchstone to detect such attitudes is to find out what is stated about the Green Revolution. Green revolution rices and wheats were one of the triumphs of conventional plant breeding. When grown in the 60s–70’s in the developing world they produced 2–3 times the yield/hectare. World cereal production doubled and oversaw a doubling of the world’s population in the last 35 years. If these green revolution cereals had not been created either we would have seen human starvation on an unimaginable level or we would have ploughed under virtually all the remaining natural forests of the world in order to produce food. The effects on global warming would have been robust to say the least. Murray is very keen to let us

know that the green revolution had some drawbacks (like all areas of human progress) but the benefits do not fit the message so do not get mentioned. Agricultural land has only increased in area some 5% in the last 50 years.

Errors are abundant. Here are just a few. Free nitrate in food is not toxic as claimed. Dietary nitrate is rapidly excreted. Salivary glands synthesise and secrete nitrate into the mouth where bacteria convert nitrate to nitrite which in the acid conditions of the stomach is converted to nitrosamines. However although nitrosamines like most natural and synthetic chemicals can be shown to be carcinogenic at high concentrations, stomach nitrosamine is far too low to have any effect.

Herbicide tolerant GM crops did not lead to a 3 fold increased use of herbicide as Murray speculates. Detailed investigations by independent agencies such as the Pew Foundation or The National Council for Agricultural Science and Technology indicated that overall use remained the same and also detailed a conversion from using less desirable herbicides like atrazine towards innocuous glyphosate. No mention by Murray either that herbicide tolerant crops lead naturally to no-till agriculture which knocks organic agriculture into a cocked hat on virtually all environmental measures used. But then Murray like many of the present zealots thinks organic agriculture, a return to the past, must be the way forward.

When a slim book spends two pages on the discredited Pusztai data, accuracy is not the prime motive for writing. No mention of somaclonal variation, the paucity of data, statistical errors, small sample sizes, that raw potato caused young rats to lose weight or that diet changes intestinal structure amongst others that led to rejection of the information in the first place. But if these had been included Pusztai would not have figured in the book at all. The Pusztai rats were not actually fed substantially equivalent diets. Sir Robert May FRS is described as a physicist with little knowledge about biology, which might surprise him since his election to the Royal Society was for ecology. Antibiotic resistance markers in GM food are suggested to give rise to antibiotic resistant bacteria despite published evidence from human feeding trials showing the contrary. Actually 10% of all soil bacteria have resistance to kannamycin, the main drug used, and soil bacteria are where the antibiotic resistance genes were obtained in the first place. Barnase (bacterial ribonuclease) is described as toxic on what evidence is not stated and none that I know of. Every meal contains ribonucleases. It is claimed that Starlink Bt maize causes allergy in humans. This was examined in the States by the FDA and CDC and discredited. We are told that GM plants are imprecise (where at least we know what DNA has been inserted) compared to conventional plant breeding where of

course we know nothing about the genetic changes. The fact that GM vitamin A-enhanced rice has been produced to reduce blindness and premature death in children escapes Murray who thinks it is instead for adults who are rarely vitamin A deficient. Prematurely weaned babies who are only fed rice gruel are the main problem. The Bt maize and the monarch butterfly is quoted as though six papers in Proceedings of the National Academy of Science USA had not thoroughly discredited the whole story. It is also stated that there is no difference between allowing transgenic maize to release pollen containing the insecticidal protein Bt and an insecticide. The Bt variant used is relatively specific for moth and butterfly larvae and such incorrect statements ignore the fact that

most insects that could be affected by insecticides do not eat pollen.

If I had purchased this text, I would be demanding my money back. I cannot imagine that anyone with any knowledge of this area would have passed this appalling catalogue of errors as fit for publication. The publisher needs to tighten up on standards and the author needs to be honest about his motives. Trying to disguise political opinions by raising specious scientific objections has caused most of the furore over GM foods. It is time it stopped and a good start would be to bin this book.

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