Mutation research

Problems, results and perspectives

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Preface

This book is intended for the senior undergraduate (Honours student) in genetics, and for the postgraduate who wants a survey of the whole field or information on a special area within it. In order to cater for readers with such different requirements, I have made the list of references unusually large for a textbook. It includes classical papers as well as very recent ones (to the end of 1974); reviews as well as specialized articles; elementary expositions from Scientific American as well as highly technical papers from journals on genetics and molecular biology. In areas of active research, I have given preference to the latest references, which will lead the reader to earlier ones. In addition to the references at the end of each chapter, a bibliography at the end of the book lists relevant books and general reviews.

Apart from the first chapter, the book is not written as a history of mutation research; but throughout I have tried to emphasize the continuity of the problems, concepts and ideas. The reader will find many examples of this. Muller's once famous and then almost forgotten classification of genes by their action has now been given biochemical reality by studies of gene action *in vitro*. The problem of whether mutations can arise in non-replicating genomes is one of the oldest in mutation research; yet an unequivocal solution was obtained only recently with bacteriophage. Bateson's presence-absence theory of mutation took long to die, especially in relation to X-rays, but was finally refuted by nucleotide sequencing. While some of the old problems have been solved by new techniques, many of them are still with us, waiting for new methods of attack. I hope that some readers will be stimulated to go back to the

classical papers, e.g. by Muller and Stadler. They will find not only beautiful work beautifully presented, but also discussions of fundamental problems in great depth and breadth.

A second truth that I want to drive home is that, in their fundamental responses to a natural or artificial mutagenic stimulus, the genes of all organisms from virus to man resemble each other. The early mutation workers never underestimated the importance of this truth, independent of whether – like Demerec – they experimented on a variety of organisms or – like Muller – remained committed to one (*Drosophila*). Muller, indeed, was the first to suggest that mutagenesis might be profitably studied in the 'naked' genes of bacteriophage. His review articles were of general validity for their time because they were based on all available evidence from macro- and micro-organims. In our age of specialization, this is no longer so. The field is now so large and diversified that it has become impossible for any one mutation worker to remain well informed about developments outside his special area. Unfortunately, however, these areas are defined by organism rather than by problem. Mutation workers consider themselves specialists on bacteriophage, *E.coli*, yeast, *Neurospora, Drosophila, Vicia faba* etc; not as being committed to the analysis of a special *problem*, even though their experiments may be restricted to one *organism*. This attitude results in general conclusions based on specialized evidence. Such conclusions may be, and often are, wrong; but they may have a long life span thanks to the same compartmentalization of interest that first gave birth to them. Wherever possible, I have tried to draw cross-connections between observations on different organisms. They are not difficult to trace: supersuppressors, unstable genes, mutagen specificity, photorepair and dark repair are among many phenomena that are encountered, and can be analysed, in a variety of prokaryotic and eukaryotic species. The freedom to choose the most suitable species for answering a special problem should stimulate cooperation between mutation workers. To be sure, there are differences between organisms in their mutational behaviour. Set against the background of an essential similarity at the primary level of DNA, these may become important tools for analysing the roles of chromosome structure, metabolic patterns and other cellular and organismal factors in mutagenesis.

This brings me to the final, and principal, point that I have stressed throughout this book: the need to realize that mutagenesis is much

more than a physicochemical reaction of environmental agents with DNA. It is a biological process and, like all other biological processes, it is deeply enmeshed in the structural and biochemical complexities of the cell. A little more than ten years ago, after the spectacular success of the molecular analysis of mutational changes in DNA, mutation research seemed to be in danger of becoming relegated to a branch of nucleic acid chemistry. Indeed, I remember a very famous geneticist saying to me at that time that the best way to study mutagenesis was to treat DNA in the test tube with a mutagen. If this were true, mutation research would now be more or less at an end; but fortunately for the research worker it is far from true. This naive picture, which never gained the allegiance of biologically-minded geneticists, broke down under the impact of findings that implicate cellular processes such as repair and replication in mutagenesis. These findings have started a new era of mutation research, with many new problems being added to the old and still unsolved ones.

In a previous book ('Mutation Methods', see Bibliography), I have discussed the rationale and basic protocols of the most important techniques in mutation research. In the present book, I have incorporated only as much methodology as seemed indispensable for an understanding of the results and conclusions. I know from teaching experience that it is tedious for the student to go through a course on methodology before he knows the particular problems that the methods are meant to solve. I have therefore inserted sections, and one whole chapter, on methods wherever it seemed required. It may be useful to list them here. Chapter 2 brings the genetic test for translocations in *Drosophila,* and the generally applicable specific-locus test for the detection of visible mutations. The best known *Drosophila* tests – the test for sex-linked lethals and the attached-X tests for sex-linked visibles and large deletions – are described in Chapter 5; the same chapter brings also the extension of the sex-linked lethal test to the detection of delayed mutations. Chapter 10 includes methods for mutation research on flowering plants, especially maize. Chapter 11 is wholly devoted to methods of mutation research on micro-organisms and cell cultures.

I owe thanks to many who have helped me with the writing of this book. First of all to my publishers, who have been understanding enough not to hustle me beyond my customary slow speed of writing. Then to their, anonymous, referees both of whom have

made very useful remarks and have rescued the book from important omissions, mis-statements and ambiguities. Several colleagues here and abroad have critically and helpfully read sections of the book, or have supplied me with information; to all of them I am very grateful. Most of all I owe thanks to my colleague, Dr. D.J. Bond, of this institute, who has read very carefully every word of the book. I am sure that without his criticism, the book would contain many more obscurities; he is not responsible for those that remain. I am very grateful to Professor D.S. Falconer for letting me use the facilities of the Genetics Department. Mr E.D. Roberts has been very helpful and ingenious in making a number of original drawings. Mrs Mardi Denell, Dr Clara Queiroz and Mrs Jacqueline Stewart have saved me much time and effort by collecting references, tables and illustrations, and Mrs Valerie Rennie has been a careful and intelligent typist. For proof-reading and the compilation of the index and glossary I have had the competent help of Dr Joan Dawes. To all these helpers I extend thanks. I also wish to thank the Leverhulme Trust for generously financing the work of these assistants through a Leverhulme Emeritus Fellowship grant.

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Illustrations