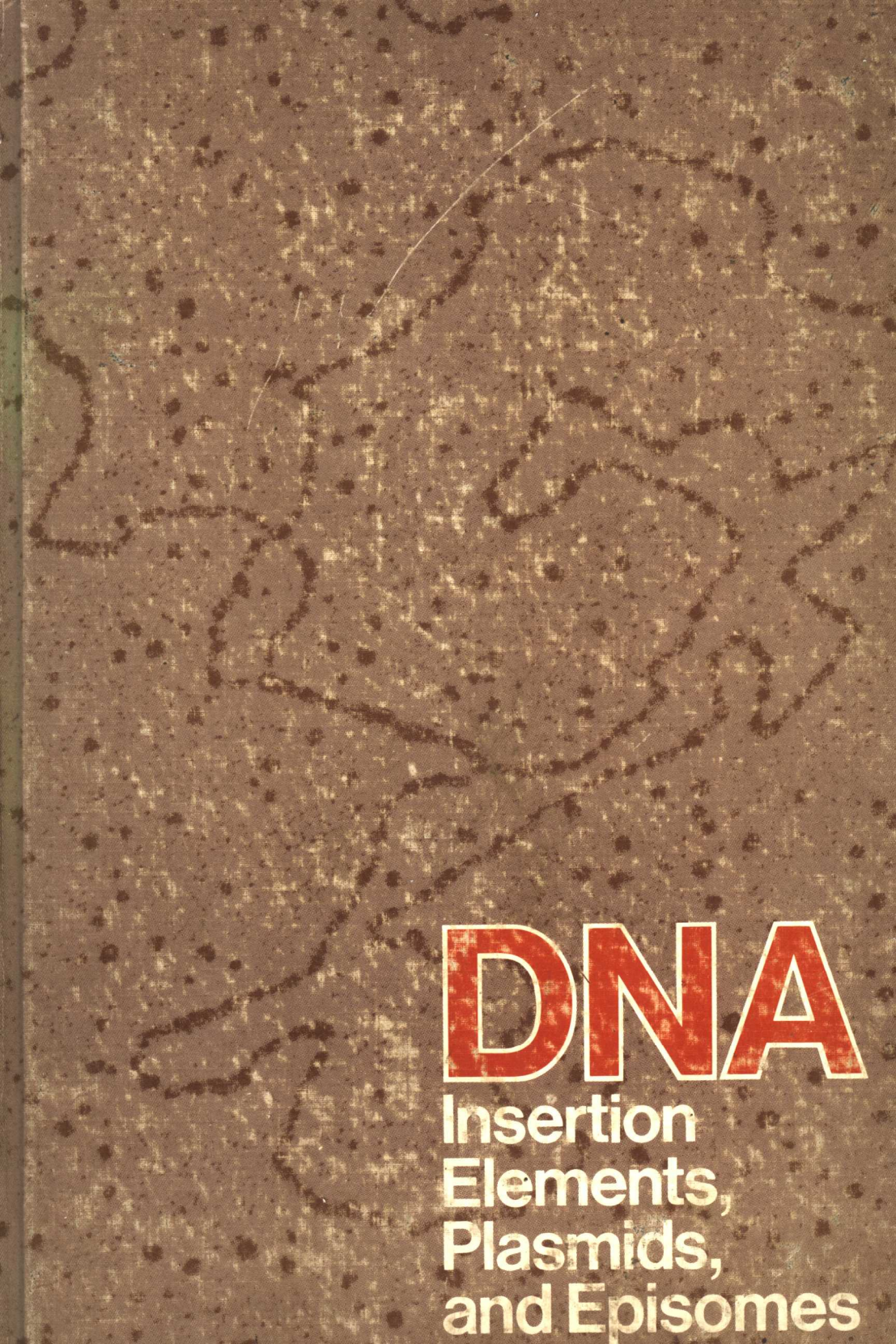
DNA
Insertion
Elements,
Plasmids,
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Edited by

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Cold Spring Harbor Laboratory 1977

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International Standard Book Number 0-87969-118-2
Library of Congress Catalog Card Number 76-57904
Printed in United States of America

Cover: An example of stem-loop structures seen when DNA from *E. coli* is denatured and reannealed. Inverted duplications, separated by unique sequences, snapped back to form these structures. In the cover picture, the stem has a length equal to that of IS*1*, 0.8 kb, and the loop consists of 13.7 kb. *(Photograph by L.T. Chow and T.R. Broker, Cold Spring Harbor Laboratory)*

DNA Insertion Elements, Plasmids, and Episomes

Preface

The Cold Spring Harbor Laboratory was the scene of an exciting meeting on DNA Insertions from May 18 to May 21, 1976. The meeting brought together biologists whose interests ranged from *Escherichia coli* to maize and from bacteriophage λ to herpesviruses. It is not possible in a scientific monograph to capture entirely the spirit of the meeting–the excitement, the inspired discussions. This book is an experiment in publishing the proceedings of a meeting. The book presents not only papers that were discussed at the meeting but also other articles and information that we hope readers will find useful. We have made an effort to scan a broad spectrum of studies and to focus on many facets of the insertion phenomena. The introduction outlines the topics covered and explains the organization of the book.

The DNA Insertions meeting and this monograph would not have been possible without the encouragement and support of J.D. Watson, Director of the Cold Spring Harbor Laboratory. The meeting was supported by funds from the National Science Foundation (PCM 76-06478), the National Cancer Institute (CA-13106), and the Cold Spring Harbor Laboratory.

We are indebted to all of our colleagues who participated in the meeting: to D. Botstein, A. Campbell, H. Lewis, M. Malamy, M. Meselson, R. Novick, J. Sambrook, A.L. Taylor, and R. Weisberg for chairing the sessions, and to S. Brenner for ending the meeting with his spirited summary. We are also grateful to B. McClintock, W. Szybalski, S. Cohen, and other colleagues for their help and advice. We are especially indebted to the authors who contributed their papers and who patiently listened to the various editorial demands.

We wish to express our appreciation to Gladys Kist of the meetings office for the meeting arrangements, to Bob Yaffee for artwork, and to Roberta Salant, Annette Zaninovic, and Judith Atkin of the publications office for help with the preparation of the book. Special thanks are due to Nancy Ford, Director of Publications, who guided the development of this book.

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SECTION V Eukaryotic Systems

SECTION VI Genetic Rearrangements; Techniques and Applications

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APPENDIX B Bacterial Plasmids

DNA Insertion Elements, Plasmids, and Episomes

Introduction: New Pathways in the Evolution of Chromosome Structure

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This book deals with a new class of genetic elements: DNA insertions. The existence of DNA insertion elements has become clear from a decade of research on the expression and structure of bacterial genomes. Recent developments indicate that DNA insertion elements serve a special evolutionary function. They mediate the integration of one segment of genetic information into another. This process is independent of previously recognized mechanisms for the interaction of DNA molecules. There are suggestions that DNA insertion elements exist not only in prokaryotic cells but also in eukaryotic cells. Thus we face the discovery of new pathways for the reassortment of genetic information and the evolution of chromosome structure in both higher and lower organisms.

Because the study of DNA insertion elements is so young, hypotheses and problems far outnumber accepted concepts. The papers in this book constitute a first attempt to define these problems and state working models to resolve them. They represent the state of knowledge about insertion elements as it stood at the time of the DNA Insertions Meeting at Cold Spring Harbor Laboratory in May, 1976. The purpose of this introduction is to explain the developments which prompted that meeting and present our view of how several different lines of research converged to define an exciting new field in genetics.

About a decade ago, the first examples of DNA insertion elements in bacterial systems were recognized in laboratories whose primary interest was the regulation of gene expression, not chromosome structure. Analysis of various operons in *Escherichia coli* revealed an unexpected class of pleiotropic mutations. They

were often located in structural genes for pathway enzymes, were neither base substitution, frameshift, nor deletion mutations, and exerted strong polar effects on the expression of other cistrons distal to the operon promoter. Eventually it was shown that these mutations resulted from the insertion of fairly large segments (700 to 1400 base pairs) of DNA into the structural or regulatory genes of these operons. Such insertions were observed in a number of genetic systems, including the *E. coli gal, lac,* and ribosomal protein operons and bacteriophage λ, P1, and P2. Further analysis of independent insertions by electron microscope heteroduplex methods revealed that many of them appear to be identical. Thus a limited number of specific DNA sequences can insert themselves into different sites in the bacterial genome to shut off gene activity. To date, repeated examples of four such insertion sequences (IS) have been documented; these have been labeled IS*1*, IS*2*, IS*3*, and IS*4*. They contain, respectively, about 800, 1300, 1200, and 1400 base pairs. A complete tabulation of these and other unclassified *E. coli* insertion mutations can be found in Appendix A1.

The discovery that the same sequences[1] can each appear repeatedly at one or more sites in the bacterial genome leads to an important conclusion: insertion mutations are not the result of random noise in the usually accurate mechanisms for replication and segregation of the genetic material. Indeed, further studies turned up many interesting characteristics of insertion sequences. The bacterial chromosome contains multiple copies of at least some IS elements. IS*1* and IS*4* exert polar effects when linearly inserted in either of the two possible ways (orientations I and II), whereas IS*2* and IS*3* are known to be polar only in one direction (orientation I). Moreover, IS*2* seems to contain a site which acts as a promoter for gene expression when present in the nonpolar orientation II. Insertion can occur at many sites but is not random, and there are "hot spots" for IS-induced mutations. The presence of some IS elements can lead to a high frequency of spontaneous deletions, which begin at the site of insertion. The one aspect of IS physiology that has received the most attention so far is the effect of insertion mutations on gene expression. We know that at least some of them are polar because they contain sites for the action of the transcription termination factor rho. Although no clear picture is yet available for all the phenotypic consequences of insertion mutations, this short list indicates that IS elements have a complex structure. Presumably, this structure is the result of natural selection for some function(s) useful to the bacterial cell. One such function could involve the control of gene expression. The papers in Section I describe the history, physiology, and structure of IS mutations.

It would be unlikely that these complex genetic elements evolved simply as mutator elements. Some clues about the normal function of IS elements have emerged from a different area of research in bacterial genetics—the study of

[1] It should be remembered that sequence identity is established by heteroduplex formation. This does not exclude small differences in nucleotide sequences.

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