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As these words are being entered on the page, bacterial toxins are not far from the headlines. In the fall of 2001 the catastrophic attacks with fuel-laden airliners on the World Trade Center towers and the Pentagon were followed by assaults with *Bacillus anthracis* spores enclosed in letters sent through the United States postal system. The perpetrator of the anthrax assaults still remains unidentified, but 11 confirmed cases of inhalational anthrax and five deaths resulted. Now, facing the threat of bioterrorism realistically, the nation is struggling to identify countermeasures to protect the population in the event of a subsequent attack with anthrax or other agents—an attack of potentially much greater magnitude than that of late 2001. As a part of this effort, attention is being focused on the toxin produced by the anthrax bacillus that makes it so deadly, and on other toxins, such as botulinum toxin, that are directly relevant to bioterrorism.

In some sense these events take us back to the era in which bacterial toxins were first discovered. Evidence that certain bacteria produce diffusible toxic substances that are responsible for disease symptoms came late in the 19th century, soon after methods for isolating and growing bacteria in pure culture were developed. Injection of culture filtrates of, for example, the diphtheria bacillus into experimental animals produced death with symptoms and lesions in internal organs characteristic of the disease. Shortly thereafter it was found that sublethal amounts of diphtheria and tetanus toxins elicited the formation of substances in the bloodstream that could specifically neutralize these toxins. Thus toxins were pivotal in the discovery of the humoral immune system of mammals. This realization soon led to toxin-based vaccine strategies and eventually to the vaccines still used today to immunize against diphtheria and tetanus.

The century-long trek from the discovery of toxins to our current understanding of their chemistry and modes of action has been integrally linked with advances in fundamental knowledge of macromolecular chemistry, cell biology, and other relevant areas. In the 1930s diphtheria toxin was purified to a sufficient extent to ascertain that it was a protein. But concepts of the nature of proteins were primitive then, and not until the 1950s did understanding of their primary, secondary, and tertiary structures become firmly grounded. Similarly, significant data on the modes of action of toxins at the cellular and molecular levels have become available only as fundamental knowledge has advanced in areas such as how proteins are synthesized, how vesicle fusion occurs in neuronal cells, etc. Clearly it would have been impossible to determine that diphtheria toxin directly
blocked protein synthesis before systems for studying this process had advanced to a certain level. As understanding of biological science has exploded in the second half of the 20th century, knowledge of toxins and their role in bacterial diseases has kept pace.

Perhaps progress in toxin research would have occurred more rapidly had it not been for certain misconceptions. In the post-World War II era, bacterial pathogenesis was not the “hot” area of research it is today. The discovery and application of antibiotics had created the widespread misconception that bacterial diseases had been conquered once and for all. Furthermore, toxins were considered odd curiosities of nature, far from the mainstream of modern biology, which was then focused on monumental questions—the genetic code, how proteins are encoded and synthesized, and the structure of proteins in three dimensions. Finally, the potential danger of working with toxins has probably always been consciously or unconsciously exaggerated in the minds of many able researchers who would otherwise have contributed to our understanding of this intriguing class of molecules.

These obstacles notwithstanding, the field of toxin research held its own through the post-World War II era, in considerable measure because of the interest of stalwart individuals such as A. M. Pappenheimer, Jr. (“Pap” to those of us who worked with him), W. E. (“Kits”) van Heyningen, and Harry Smith. How a purified, potentially lethal toxin acted seemed to provide the most straightforward route to answer the question of how a bacterium could kill a human being.

As fundamental knowledge advanced in the 1960s and 1970s, seminal discoveries were made regarding the biochemical modes of action of several protein toxins—notably diphtheria, cholera, *Pseudomonas* exotoxin A, and the ricin family of plant toxins. Interest in these molecules grew as it became evident that a sizable fraction of bacterial and plant toxins were extraordinary enzymes having the capacity to enter mammalian cells and modify substrates within the cytosolic compartment. Hence, these proteins had the rare property of being able to cross membranes at some level. This fascinating property, combined with their interesting catalytic activities (e.g., ADP-ribosylation), brought toxins to the attention of mainstream biological researchers and made these proteins useful as tools to probe important metabolic pathways and processes.

In 1972 the first Gordon Conference on Bacterial Toxins was held (chaired by Sam Ajl), and the Conference has been a biennial event ever since. The European Workshop on Bacterial Protein Toxins came into existence later and has been held in various countries in alternate years. Fostering the exchange of ideas and advances in the area, these meetings have greatly elevated the stature of the field. As better methods to study the diverse array of virulence factors used by bacteria have evolved in recent years, interest in other aspects of bacterial pathogenesis has greatly increased, and the subject matter addressed in these conferences has broadened correspondingly. For decades toxins were about the only determinants of pathogenicity accessible to investigation. Now, all that has been changed by modern tools of biology.

The advent of recombinant DNA technology had a profound effect on toxin research, as it did on almost every other aspect of biology. Clearly the possibility of cloning and expressing a toxin in a heterologous organism required caution and regulation. Indeed, cloning of the most potent toxins (e.g., the clostridial
neurotoxins) is still prohibited. Nonetheless, as structure-function relationships of various toxins were elucidated, it became evident that they were complex proteins and that certain parts were benign in the absence of the complementary parts. This allowed selected domains of the highly potent toxins to be cloned under minimal containment conditions and, in turn, permitted approaches such as directed mutagenesis and creation of chimeric molecules to be implemented. Among the results are “recombinant toxoids” and new types of targeted toxins.

The notion that a toxin might be used to generate a “magic bullet” that could target a specific tissue or subset of cells in the body is an old one that emerged in a new form in the 1980s. The concept of AB toxins, containing an enzymatic A moiety linked by a disulfide bridge to a receptor-binding B moiety, a motif found in many toxins (e.g., diphtheria and ricin toxins), immediately suggested a way to direct the action of these proteins to specific cells. Early attempts involved generating disulfide-linked chimeras containing, for example, the A chain of diphtheria or ricin toxin linked to a monoclonal antibody directed towards a tumor-specific antigen. Such chimeras were generally less potent and specific than hoped, but the early attempts in this direction generated widespread interest. Subsequently there have been isolated successes, including a recombinant chimeric toxin against T cells that has recently been licensed by the FDA for treatment of certain types of tumors.

The past two decades have witnessed the discovery of many new toxins and toxin-like virulence factors (e.g., the effectors introduced into cells by type III secretion systems), and their numbers will undoubtedly grow as the genomic sequences of bacterial pathogens are determined. The diverse strategies adopted by bacteria to subvert the cellular biochemistry and physiology of the host have provided tools for use in cellular and molecular biological investigations, new targets for drug development, and a better understanding of the selective advantages accruing to bacterial pathogens from toxin production. Over the same period, our understanding of the classical toxins has extended to finer levels of detail. The crystallographic structures of many of these molecules have been solved, providing a framework to understand how they recognize receptors, penetrate membranes, and recognize and modify substrates. This said, there is still no toxin for which we can claim a complete understanding, and for most of them, major gaps remain in our knowledge.

Now, at the beginning of the 21st century, we have in a sense come full circle. Despite the advances made over the past century, multiple threats—bioterrorism, the spread of antibiotic resistance, and the emergence of new bacterial pathogens—keep knowledge of bacterial virulence a subject as crucial to the health of mankind as it was at the beginning of the 20th century. This volume presents an excellent summary of current knowledge of bacterial toxins and will serve as a major resource for current practitioners and new students entering the field in the coming years. I wish them the thrill of discovery and the camaraderie with outstanding students and colleagues that I have experienced throughout my career.

R. John Collier
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PREFACE

For the past three decades, our understanding of the molecular aspects of bacterial toxins has grown exponentially. The seminal studies that identified diphtheria toxin as a protein with the intrinsic capacity to enter eukaryotic cells and inhibit protein synthesis through the posttranslational modification of a single eukaryotic protein provided a platform for studies on other medically important bacterial toxins. Initially, experts in protein structure, enzymology, and electrophysiology were drawn into our field to study toxin action, while more recent additions to our field have included cell biologists and investigators who study eukaryotic signal transduction. The study of bacterial toxins demands an integration of distinct fields of investigation, providing a synergy for our understanding of toxin action.

The initial concept of this book was spurred by our desire to provide a succinct reference source for students interested in bacterial toxins. The goal was to integrate historical experiences and contemporary concepts of toxin biosynthesis, structure, and function. One important concept that the authors share with students beginning their studies on bacterial toxins is the importance of pursuing quantitative analyses of toxins. This approach has allowed our field to advance to its current level of sophistication. The chapters include both written and pictorial representation of major concepts, provide references for additional reading, and are written by investigators who have direct expertise in the area. The book is divided into five sections which address (i) the genetics and regulation of toxin gene expression; mechanisms for toxin translocation across (ii) bacterial and (iii) eukaryotic membrane barriers; (iv) descriptions of toxins that covalently modify host target proteins and recently recognized toxins that modulate host protein function by noncovalent mechanisms; and (v) the current status of both the beneficial and harmful uses of bacterial toxins.

The study of bacterial toxins has led to novel strategies that use these toxins for medical purposes. However, in October of 2001, we witnessed the deplorable use of a bacterial organism as a reagent for terrorism, by an individual(s) who disregarded the ethical standards of our society. It is our obligation to work towards the beneficial use of bacterial toxins as vaccines, antidotes, and therapies.
This is the challenge we present to our junior microbiologists, and we provide this text as a reference for your studies.

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