MANUAL OF
Industrial Microbiology and Biotechnology

SECOND EDITION

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Arnold L. Demain and Julian E. Davies

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Wei-Shou Hu, David H. Sherman, Richard C. Willson,
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Preface

Jackson W. Foster once said, "Never underestimate the power of the microbe." Demain and Solomon's *Manual of Industrial Microbiology and Biotechnology*, published by ASM Press in 1986, helped workers in the field harness the industrial "power of the microbe." That first edition has become a classic, and not just because it is now on the bookshelves of most microbiology laboratories with covers stained and pages well thumbed. "Demain and Solomon" was the forerunner of other manuals of microbiology outside of medical practice. This Second Edition has been expanded to include still more information on applications of molecular biology, not in an attempt to compete with Maniatis and others, but to provide more information on modern technical advances in the study and application of microorganisms to industrial situations. Areas covered in the First Edition are included, but the chapters have been written by new authors in an up-to-date manner. None of the original chapters remains.

Much has changed in the past decade; *Escherichia coli* and *Saccharomyces cerevisiae* have become industrial workhorses in a way no one could have predicted. New organisms have entered the biotechnology workplace to compete with these two stalwarts. Thus, covered in the Second Edition are *Bacillus*, actinomycetes, non-*Saccharomyces* yeasts, filamentous fungi, insect cells, mammalian cells, and plant cell culture. The genetics of thermophiles and other extremophiles, pseudomonads, and corynebacteria are also included. New techniques of combinatorial biosynthesis, metabolic engineering, directed evolution of enzymes, gel microdroplet technology, and informatics have been added.

Nothing can be like the original; it has been our goal, with the help of our section editors and authors and the encouragement (otherwise known as constant prodding) of ASM Press (Ellie Tupper, Greg Payne), to bring the *Manual of Industrial Microbiology and Biotechnology*, Second Edition, into a millennium format by broadening coverage. For example, recombinant DNA applications as applied to aromatic compounds and polyhydroxyalkanoates (PHAs) have been added as well as chapters on biodiversity, bioprospecting, bioremediation, biofilms, and release of recombinant microbes into the environment. Data analysis, contract fermentations, and quality assurance and quality control are now included. Greater emphasis has been given to aspects of secondary metabolism such as studies of resistance, regulation, and biosynthesis; bacteriocins; downstream processing of small and large molecules; and protein production and secretion. Perhaps this increased coverage has resulted in providing fewer recipes, but we believe that answers to all technical questions can be found in the references provided with each article.

This Second Edition should be of great use to all members of our field, including students, postdoctoral associates, faculty, technicians, senior researchers, factory personnel and managers, research and development managers, top management, patent agents, and technology transfer personnel. It is hoped that the manual finds its way into offices, laboratories, and university libraries, as well as pharmaceutical, chemical, energy, and food companies and the thousands of biotechnology companies and institutes throughout the world. If so, we will derive great satisfaction in that all who participated in this volume have helped to contribute to the spirit expressed by Louis Pasteur: "Non, mille fois non, il n'existe pas une catégorie de sciences auxquelles on puisse donner le nom de sciences appliquées. *Il y a la science et les applications de la science*, liées entre elles comme le fruit à l'arbre qui l'a porte." ("No, a thousand times no, there does not exist a category of science to which one can give the name applied science. There is science and the applications of science, bound together like the fruit carried on a tree.")

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Editors in Chief

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CULTURES

I

ALMOST ALL INDUSTRIAL MICROBIOLOGY PROCESSES REQUIRE THE initial isolation of cultures from nature, followed by small-scale cultivations and optimization, before large-scale production can become a reality. The chapters in this section deal with the most essential element of any fermentation process, the culture. They describe how to isolate cultures from nature, screen for biological activities, develop high-quality inoculum, carry out small-scale fermentations, and effectively improve and store the cultures.

Microorganisms, with their extremely diverse metabolic activities, represent an almost unlimited source of biological activities for industrial applications. The first chapter of this section, "Isolation of Cultures" by Hunter-Cevera and Belt, describes general procedures and media for collecting and isolating microorganisms from nature, including filamentous bacteria (actinomycetes), bacteria, and fungi. In the following chapter, "Screening for Activities," Huang et al. present methods for screening cultures for desired biological activities, using several industrial cases as examples.

After the desired culture is obtained, maintenance of the essential characteristics during long-term culture storage is crucial. The procedures and media for preserving various microorganisms are outlined in the chapter "Culture Preservation and Inoculum Development" by Monaghan et al., who also describe methods for developing inoculum from a preserved culture.

Once a culture producing the desired product is obtained, the feasibility of large-scale production is first tested in small-scale fermentors. Hilton describes fermentation equipment and methods in his chapter "Small-Scale Liquid Fermentations." Although liquid fermentation is used in most industrial fermentations, solid-state fermentation remains the method of choice for many traditional industrial processes, particularly for the food industry. The subsequent chapter, "Small-Scale Solid-State Fermentations" by Sato and Sudo, describes the methods for this type of fermentation, including fermentor design and process control strategies.

Small-scale fermentations provide an economical means for examining a large number of fermentation parameters for process optimization, largely through empirical approaches. One of the most important parameters is the medium, which contains various components regulating the production of the desired product. In their chapter "Experimental Design for Improvement of Fermentations," Strobel and Sullivan present experimental design and statistical analysis techniques for analyzing combinations of nutritional as well as nonnutritional parameters for rapidly improving a fermentation process. Several hypothetical models and authentic case studies are presented to illustrate the design techniques.

Besides growing cells, immobilized microbial cells or extracted enzymes can be used for production of the desired product. Tanaka and Kawamoto describe various methods for immobilizing cells and enzymes in their chapter "Cell and Enzyme Immobilization." The subsequent chapter deals with strain improvement. In addition to process optimization, successful industrialization of a fermentation process always depends on genetic improvement of strains. Despite the development of recombinant DNA techniques, the use of nonrecombinant methods for strain improvement remains important, particularly for organisms lacking well-developed genetic tools. Vinci and Byng present key methods for mutagenesis and subsequent screening for improving cultures in their chapter, "Strain Improvement by Nonrecombinant Methods." The recombinant approach for strain improvement is addressed in a different section of this manual.

Finally, this section includes two special chapters. Weaver describes a flow cytometric technique enabling culture of microbial cells and functional and compositional measurement at the individual cell level in his chapter, "Culture and Analysis Using Gel Microdrops." In the last chapter of the section, "Cultivation of Hyperthermophilic and Extremely Thermoacidophilic Microorganisms," Rinker et al. address culture methods for extremophiles, which are important sources of thermostable enzymes.