BIOTECHNOLOGY & PHARMACY

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Biotechnology and Pharmacy

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Preface

During the 10 years that have elapsed since FDA approval of recombinant human insulin, over 100 products derived from biotechnological processes have progressed to the stage of clinical use or human trials. Over the next 10 years, global sales of biotechnology products are expected to approximate $30 billion per annum. It is therefore abundantly clear that the practice of pharmacy has been, and will continue to be, strongly influenced by the field of biotechnology and that the practicing pharmacist should have a firm understanding of the area. Because it is a relatively new field of scientific endeavor, however, traditional pharmacy curricula have not included comprehensive coverage of basic biotechnology or the resulting products and processes. Bearing these factors in mind, we have assembled *Biotechnology and Pharmacy*. It is anticipated to be of key interest to pharmacy students and practicing pharmacists who have not had extensive exposure to the field of biotechnology but who have received basic training in biological sciences (e.g., biochemistry, genetics) at the undergraduate professional level. The book should also be of value to other health professionals such as physicians, dentists, and nurses, who are interested in an overview of this important field of science. In addition, graduate students in the biological sciences should benefit by its use.

Biotechnology and Pharmacy has been organized into three parts: "Basic Elements of Biotechnology," "Applications of Biotechnology in the Pharmaceutical Sciences," and "Biotechnology and the Practice of Pharmacy." The chapters in these sections tend logically to fall into these groupings, but it is not necessary to peruse the parts or chapters in a sequential manner. Each chapter was prepared in a stand-alone manner, employing cross-references when appropriate to avoid redundancy. The text in its entirety is intended to provide a reasonably comprehensive overview of the history of many key elements of biotechnology, as well as a comprehensive description of the current state of the field and an indication of future trends. The text should also provide a solid foundation for more advanced studies in a number of related areas.

This volume developed through a faculty retreat and symposium on biotechnology supported through the Grant Awards for Pharmacy Schools program conducted by the American Association of Colleges of Pharmacy and funded by SmithKline Beecham. We gratefully acknowledge the financial support that made this work possible. We are also grateful to Carol Lewandowski and Martha Hoskins for assistance in many areas during the production of this volume.

Chicago
January 1993

J.M.P.
M.E.J.
H.R.M., Jr.

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SECTION I

Basic Elements of Biotechnology

1

Background to Recombinant DNA Technology

Leonard G. Davis

1.1. Introduction

This chapter serves as a basic primer for those not familiar with the principles and techniques used in molecular biology and is not designed for those already aware of its value. It will emphasize terminology and provide general descriptions of the procedures, with a primary focus on why molecular biology is having such an impact (some call it a revolution) on biological studies. The chapter will also include a few scientific examples, since it is worth emphasizing that these techniques are best utilized as a complement of current approaches designed to answer research questions. Until a few years ago these techniques were employed mostly in academic investigations of the basic mechanisms of cell function. In a few cases they were applied by small biotechnology companies that sought to utilize the procedures for the production of bioactive proteins for use as potential drugs, rather than the typical heterocyclic organic chemicals. More recently this technology has been recognized as a powerful tool for facilitating more classical pharmaceutical and drug development efforts. The reader is, however, referred to the other chapters for more detailed examples, especially of pharmaceutical applications. For descriptions beyond the concise presentation necessitated herein, the reader is referred to some excellent books on the subject (for textbook descriptions, see references 1 to 3; for methodology, see references 4 to 7).

A convenient starting point is to recall the Central Dogma of Biology,[8] which dictates that information for the development, organization, and function of living systems is stored in discrete units (genes) within the linear deoxyribonucleic acid (DNA) molecules (chromosomes) of each cell.[9] At appropriate times, portions of the DNA information are transferred by transcription from the gene into linear ribonucleic acid (RNA) molecules for translation into functionally active proteins (see Figure 1.1). The basic building blocks used for DNA are four nucleotides (2-deoxyriboses linked through the 1 position to one of the nucleic acid bases, guanine [G], thymine [T], cytosine [C], or adenine [A]), which are linked to each

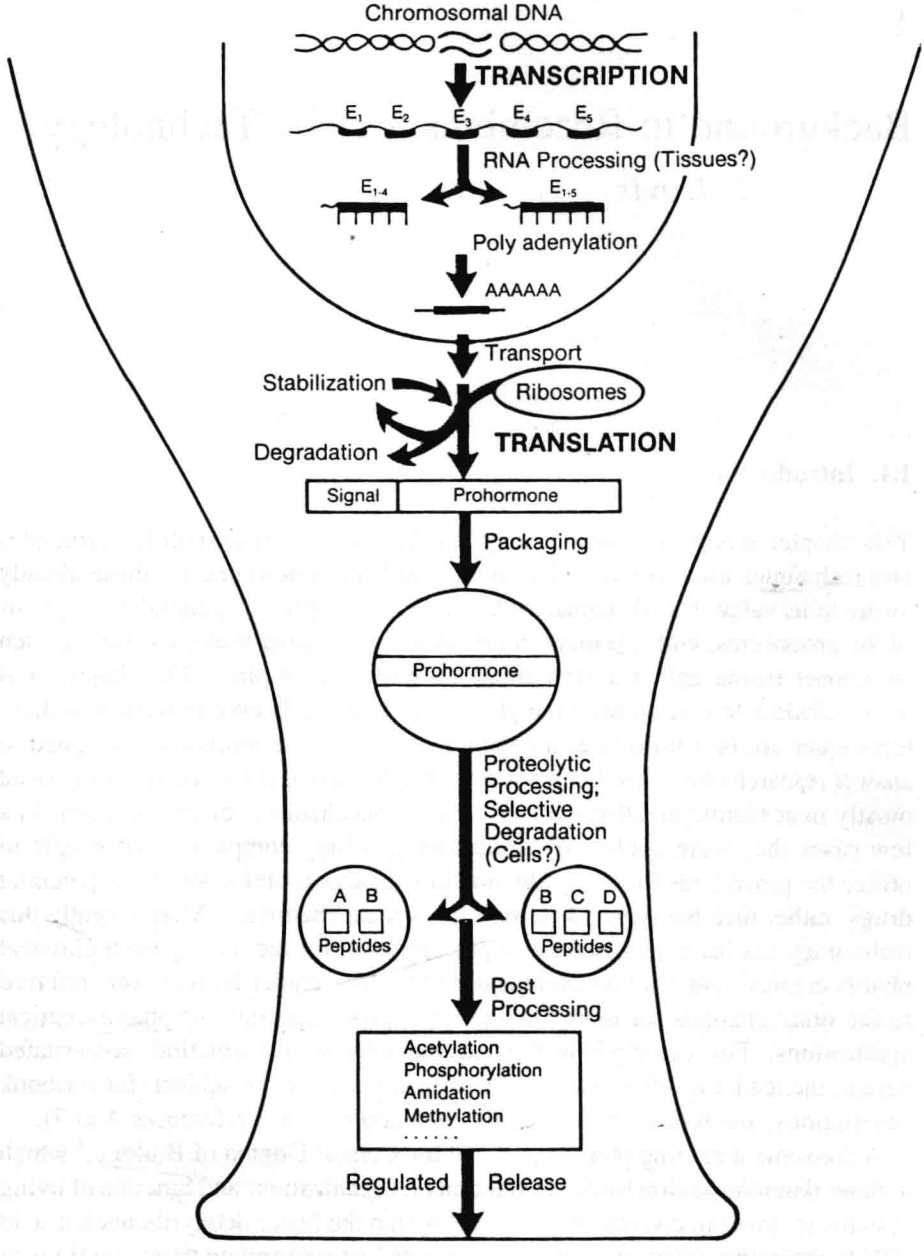

Figure 1.1. Schematic depicting the flow of information within a cell. The example used is a neuron that is generating a peptide neurotransmitter.

other in the linear DNA molecule through a phosphate ester bond at the 5′ position of the deoxyribose of one nucleotide to the 3′ position of the deoxyribose moiety on the adjacent nucleotide. DNA exists as a double helix with one linear strand proceeding in the 5′ to 3′ direction and the other aligned parallel to it but in the opposite orientation (i.e., 3′ to 5′). The two strands are held together by hydrogen bonding, in which Cs pair with Gs and Ts pair with As. The resulting DNA forms two complementary strands such that the sequential order of the nucleotides of one of the strands (a gene) can be exactly copied into a messenger RNA (mRNA) molecule (copying of both strands occurs in cell duplication).

RNA also uses four nucleotides (uridine is used in place of thymidine) that are attached to ribose (no deoxy positions) and the same 5′ to 3′ covalent phosphoester linkage between adjacent riboses is used as the backbone of the polymer. These RNA units are linear and single stranded, since their synthesis depends upon the opening of the double-stranded DNA where RNA polymerase copies one strand through the use of the base pairing principles. This ensures that an exact complementary copy of the DNA exists as RNA. In most lower organisms (prokaryotes) the exact copy of the DNA information is represented in the RNA and directly codes for proteins; in higher organisms (eukaryotes) this linear RNA copy of the DNA contains regions that code for amino acids (called exons, since they are excised for use; see Figure 1.2) and intervening sequences of DNA that apparently do not code for the protein (called introns).

The RNA (after processing to remove introns in eukaryotes) then serves as the template (as mRNA) for translation into a protein molecule. The mechanism of converting linear nucleotide sequence information into a linear array of amino acids (proteins) depends upon the recognition of a nucleotide triplet (usually AUG for methionine) near the 5′ end of the mRNA, which encodes the first amino acid (N-terminal). Each amino acid is carried by small transfer RNA molecules, each possessing a specific recognition site triplet (again complementary base pairing is used). The transfer RNA triplet complementary for the next three nucleotides in the mRNA binds and transfers its amino acid to the growing polypeptide chain. Consecutive triplets of nucleotides determine the orderly sequence of the amino acids until a stop codon (e.g., UAG) is found in the reading frame. The complete translation of mRNA occurs in the ribosomes (a RNA and protein complex) and results in a cellular protein. These proteins can then be posttranslationally modified (i.e., through phosphorylation, glycosylation, etc., of specific amino acids) and folded into three-dimensional topological units. The proteins serve many functions within the cell, ranging from the enzymatic machinery of energy metabolism and structural components of the membrane to the very specialized functions of different cell types (e.g., neurotransmitters for neurons, hormones for endocrine cells, and myosin for muscle cells). What is important here is that the Central Dogma and the triplet coding system are consistent from bacteria to humans; thus, the tools developed over many years of research by microbiologists can also be utilized.