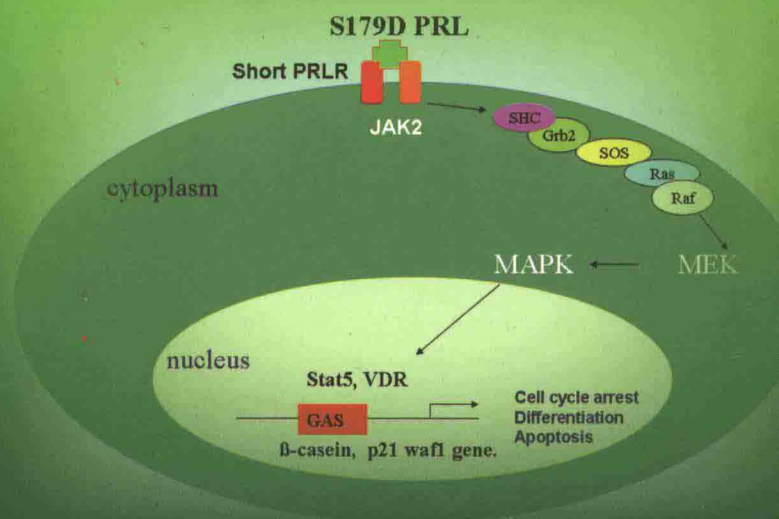




Molecular Biology

Chief Editors Wei Wu Yuxiang Zhang

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Molecular Biology

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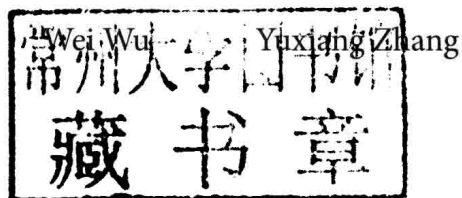
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Foreword

Global developments in medicine and health shape trends in medical education. And in China education reform has become an important focus as the country strives to meet the basic requirements for developing a medical education system that meets international standards. Significant medical developments abroad are now being incorporated into the education of both domestic and international medical students in China, which include students from the districts of China's Hong Kong, Macao and Taiwan that are taught through mandarin Chinese as well as students from a variety of other regions that are taught through the English language. This latter group creates higher demands for both schools and teachers.

Unfortunately there is no consensus as to how to improve the level and quality of education for these students or even as to which English language materials should be used. Some teachers prefer to directly use original English language materials, while others make use of Chinese medical textbooks with the help of English language medical notes. The lack of consensus has emerged from the lack of English language medical textbooks based on the characteristics of modern medical education in China.

In fact, most Chinese teachers involved in medical education have already attained an adequate level of English language usage. However, English language medical textbooks that reflect the culture of the teachers would in fact make it easier for these teachers to complete the task at hand and would improve the level and quality of medical education for international students. In addition, these texts could be used to improve the English language level of the medical students taught in Chinese. This is the purpose behind the compilation and publishing of this set of English language medical education textbooks.

The editors in chief are mainly experts in medicine from Capital Medical University (CCMU). The editorial board members are mainly teachers of a variety of subjects

from CCMU. In addition, teachers with rich teaching experience in other medical schools are also called upon to help create this set of textbooks. And finally some excellent scholars are invited to participate as final arbiters for some of the materials.

The total package of English medical education textbooks includes 63 books. Each textbook conforms to five standards according to their grounding in science; adherence to a system; basic theory, concepts and skills elucidated; simplicity and practicality. This has enabled the creation of a series of English language textbooks that adheres to the characteristics and customs of Chinese medical education. The complete set of textbooks conforms to an overall design and uniform style in regards to covers, colors, and graphics. Each chapter contains learning objectives, core concepts, an introduction, a body, a summary, questions and references that together serve as a scaffold for both teachers and students.

The complete set of English language medical education textbooks is designed for teaching overseas undergraduate clinical medicine students (six years), and can also serve as reference textbooks for bilingual teaching and learning for 5-year, 7-year and 8-year programs in clinical medicine.

We would like to thank the chief arbiters, chief editors and general editors for their arduous labor in the writing of each chapter. We would also like to acknowledge all the contributors. Finally, we would like to acknowledge Higher Education Press. They have all provided valuable support during the many weekends and evening hours of work that were necessary for completing this endeavor.

President of Capital Medical University
Director of English Textbook Compiling Commission
Zhaofeng Lu
August 1st, 2011

Preface

With the development of biology and biological techniques, a new edged discipline, called molecular biology, began to emerge in the mid-1900s. It is, however, an elusive term that has different definition dependent of who is doing the defining. In this textbook we adopted the definition by Dr. Rob Weaver, a professor of biochemistry and the Dean of the College of Liberal Arts and Sciences, University of Kansas, that molecular biology is the study of genes and their activities at the molecular terms, including transcription, translation, DNA replication, recombination and translocation, and related technologies. As a new period, during which experimental researches focus on the roles of macromolecules such as nucleic acids (including gene/DNA and RNAs) and proteins (including enzymes) in genetic transmission, molecular biology is often described as the third stage of biochemical development. Sometimes, it is also referred to as biochemical genetics. Therefore, it is easily recognized that the emphasis of molecular biology focuses on structure, organization, and regulation of genes, by which scientists study the nature of life processes. Its ultimate purpose is to discover how and to what extent such characteristic manifestations of life as heredity, reproduction, biosynthesis of proteins, excitation, growth and development, storage and transfer of information are determined by the molecular structure, properties, and interactions of biologically important substances, primarily of the two principal classes of macromolecules—proteins and nucleic acids.

This book begins with a briefly historical review of molecular biology in Chapter 1. Chapters 2 and 3 involve genetic materials and genetic information transmission and its regulation. Chapter 4 focuses on DNA damage and repair. Chapter 5 focuses on protein sorting and processing. Chapters 6–8 present the useful methods in molecular biology. Chapter 9 involves the concepts of gene transfer and gene targeting. Indeed, one of the most important practical problems that molecular biology is expected to provide answers for is the molecular basis of malignant growth. This book, therefore, is ended by Chapter 10, molecular biology of cancer, which gives students examples of how molecular biology is implicated in medical sciences. It is hoped that molecular

biology will also discover ways of preventing and perhaps conquering “molecular diseases”. The prospects in molecular biology are quite huge today. It covers a wide variety of fields and provides answer to almost every area of sciences such as molecular evolution, molecular virology, molecular immunology, and biomedicine.

As the bioinformatics and microarray develop (see Chapter 8), molecular biology comes to a big stride in screening and diagnosis of genetic and molecular diseases, gene targeting, transgenic animals and gene therapy. Thus, it is essential to study those techniques for undergraduates and graduates to have a good understanding in contemporary medicine and biology. This book is just for meeting these requirements.

Finally, we thank all members of our project team. Thanks to the Administration of Teaching and Education Management, CCMU and Higher Education Press, China, for their supporting in writing and publishing this book. In particular, we thank the readers for improving suggestions for next edition.

Hongti Jia
January, 2014

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Historical Review of Molecular Biology

- 1.1 Definition of Molecular Biology
- 1.2 Brief History of Molecular Biology
 - 1.2.1 Stage I: from the Second Half of 19th Century to the End 1940s
 - 1.2.2 Stage II: from 1950s to 1970
 - 1.2.3 Stage III: from 1970s and Continued
- 1.3 Basic Content of Molecular Biology
- 1.4 Role of Molecular Biology in Medical Science
 - 1.4.1 Cancer Research
 - 1.4.2 Study of Genetic Diseases
 - 1.4.3 Drug and Vaccine Development

▪ Objective

To understand what is “molecular biology” and the role of molecular biology in life sciences, especially in medical science.

▪ Key Concepts

Molecular biology; Biological macromolecules

▪ Introduction

In 1940, “one gene-one enzyme” hypothesis was proposed to explain genetic function in biochemical terms, which brought the sciences of genetics and biochemistry into a special relationship, called biochemical genetics. In 1944, studying the phenomenon of transformation in bacteria showed DNA as genetic material. In 1953, the double-helical model of DNA revealed both the chemical nature and the molecular structure of the unit of heredity. Consequently, the gene/DNA and its function (replication, transcription and translation) were amenable to analysis at a molecular level. The researches on macromolecules including DNA, RNA and protein syntheses (replication, transcription and translation) and their structures revolutionized the study of biology in 1950s–1960s. Thus, the term of molecular biology emerged as the times required. Today, molecular biology as the third stage of biochemistry occupies a key position in life sciences. The ever-increasing importance of molecular biology can be seen by a briefly historical review of molecular biology in this chapter.

1.1 Definition of Molecular Biology

The term of molecular biology has different definitions. In a broad sense, molecular biology is a science discipline studying the nature of all sorts of biological phenomena in molecular terms. Markedly, this definition makes it difficult to distinguish

from traditional biochemistry. In the narrow sense, molecular biology, which is sought to be the third stage of development of biochemistry, is to study genes and their activities in the molecular level. Indeed, explaining genetic function in biochemical terms brought the sciences of genetics and biochemistry into a special relationship (known as **biochemical genetics**) and added new dimensions to the research in both disciplines. Thus, we can also say, molecular biology is to understand genetic function through research on the **biological function and molecular function of biological macromolecules** in living, including gene (DNA), RNA, and protein. The modern advancements in biochemistry, genetics, microbiology, virology, and cell biology with their crossover in various research fields gave birth to molecular biology, and rapidly accelerated its emerging to many branches of biological and medical academics. During the researches in molecular biology, a well-defined system of principles and related technologies has been established.

1.2 Brief History of Molecular Biology

It is generally agreed that the development of molecular biology as a scientific branch can be described in three stages, each of which with its important breakthroughs and monumental events.

1.2.1 Stage I: from the Second Half of 19th Century to the End 1940s

Since molecular biology grew out of the disciplines of genetics and biochemistry, it is necessary to backtrack in time to briefly review the history of genetics, although it cannot be considered molecular biology and even molecular genetics. The so-called **transmission genetics** deals with the transmission of traits from parents to their offspring. That is, each parent contributes **genetic units** to the offspring. Later, scientists called the genetic units as **genes**.

In 19th century, the development of biological researches gradually moved forward from whole organism to cellular, and then to the molecular level. Proteins and nucleic acids (DNA and RNA) have been demonstrated to be polymers consisting of amino acids and nucleotides, respectively. In 1940, George Beadle and Edward Tatum (joint Nobel Prize, 1958) suggested “**one gene-one enzyme**” theory, arguing that each gene was responsible for the structure of one, and only one, enzyme. In 1944, Oswald T. Avery and his

colleagues studied the phenomenon of **transformation** in bacteria, and identified DNA as the transforming principle. At that time, understanding of genetic function in biochemical terms brought the sciences of genetics and biochemistry into a special relationship, called **biochemical genetics**.

1.2.2 Stage II: from 1950s to 1970

Research on macromolecules in the 1950s revolutionized the study of biology. In 1950, Astbury from England used the term of “**molecular biology**” to indicate a general strategy that many biomedical scientists started to pursue at the time, which was to reveal the nature of life through the structural and functional studies of such large biomolecules.

The identification of DNA as genetic material by Avery was not universally accepted until the early 1950s. In 1953, James D. Watson and Francis H. C. Crick (joint Nobel Prize, 1962) elucidated the structure of DNA, the **double-helical model**. With the announcement of the DNA model, both the chemical nature and the molecular structure of the unit of heredity were hypothesized. The gene (DNA) and its function (DNA replication, RNA transcription, and protein synthesis) were amenable to analysis at a molecular level. Therefore, the discovery of DNA double-helical model is often referred to as the beginning of molecular biology.

In the following years, the DNA researches began to dominate the focus of molecular biology. Within a mere 20 years of time, a series of important breakthroughs, including the discovery of messenger RNAs (mRNAs), the decipherment of the genetic codes, together with the discoveries of DNA polymerase, RNA polymerase, restriction endonuclease, ligase, and DNA delivery vectors of plasmid, etc, eventually gave birth to the technology of DNA recombination in the 1970s. To allow a better understanding of the establishment and development of molecular biology, let us overview and outline chronologically some of the important historical events or achievements.

The 1950s was a productive period for the study of proteins. In 1951, Linus Pauling (1954 and 1962, Nobel Prize) and Robert B. Corey proposed the **α -helical conformation** as secondary protein structure. In 1953, Frederick Sanger (1958, Nobel Prize) published the 51 amino acid sequence of insulin. The latter part of the 1950s also began to yield the answer of how amino acids incorporated into protein/polypeptide.

In 1958, Matthew Meselson and Franklin Stahl proved the DNA replication in bacteria follows the **semiconservation pathway**. In 1959, Uchoa, an US scientist of Spanish descent, discovered an enzyme of polynucleotide phosphatase and successfully synthesized nucleic acid. He used the artificially synthesized products to reconstitute a system and demonstrated the process of DNA passed the genetic information to direct the translation of proteins through necessary intermediates. He shared the 1959 Nobel Prize in Physiology and Medicine with Arthur Kornberg who discovered the **DNA polymerase** from *E. coli* and made key contribution to the *in vitro* **replication** of the bacteria.

From 1961 to 1966, Marshall Nirenberg (1968, Nobel Prize) and Har Gobind Khorana decoded the entire set of the **genetic code**, which is universal to lives. Therefore, the mystery of how genetic information on the DNA to be transmitted to the sequence of translated proteins was finally resolved. In 1965, Francois Jacob and Jacob Monod from France were laureated the Nobel Prize in Physiology and Medicine with their discovery of the “**operon**” for the regulatory mechanism of metabolism in bacteria (1961). Jacob and Monod also proposed a nucleic acid intermediate that complements with the chromosomal DNA sequence and transcodes the information at the places of protein biosynthesis. The molecules that can direct the protein translation are termed as the messengers, i. e. mRNAs. This theory was of great importance for the development of molecular biology.

In 1964, Littlefield et al used HAT selection medium to overcome the problem in the selection and screening of hybridoma cells. The HAT selection medium is designed according to the metabolic pathways of inosine or pyrimidine nucleotide biosynthesis. In 1967, five different laboratories in the world have discovered the **DNA ligase** at approximately the same time. In 1970, an enzyme with much higher activity of the same kind was identified, known as the T4 DNA ligase.

1.2.3 Stage III: from 1970s and Continued

The rapid development and wide applications of **recombinant DNA technology** is the key establishment of this stage of molecular biology in history. This technology enabled the molecular biologists to cut and join DNA fragments *in vitro* at will, or produce desired DNAs in large quantities, and in return,

rapidly improved the research on DNA structures and functions. With the help of DNA recombination, molecular biology has entered into a new era, where people not only better understood the biology of organisms, expanded the applications, but also acquired the ability to modify or even create novel living species.

In 1970, the first **restriction endonuclease** was separated and characterized. In the meantime, Howard Temin and, simultaneously, David Baltimore (joint Nobel Prize, 1975) discovered the **reverse transcriptase**, a **RNA-dependent DNA polymerase** that makes a DNA copy of RNA genome of retrovirus. In 1972, Khorana's group synthesized the entire tRNA gene. Paul Berg successfully completed the very first *in vitro* DNA recombination experiment in the world. These marked the beginning “**genetic engineering**” as a core technology. In 1973, Herb Boyer and Stanley Cohen firstly proposed the principle of **molecular cloning** (also known as **DNA cloning**) based on their experiments. They used a **plasmid vector** (pSC101) that contains a single *EcoRI* restriction site, and linearized the DNA by digestion. Then, another linearized DNA plasmid fragment generated by the digestion of the same restriction enzyme was conjugated to the vector with the help of DNA ligase. Thus, a new vector with two replication origins was obtained. This has become the first attempt for engineered recombination of DNAs. As soon as the cloning strategy was established, the biologists immediately recognized its importance and great potential of such techniques. The DNA recombination revolutionized studies of biological sciences of various fields as it was being improved. Under its powerful influence, the research of life science has quickly moved forward from the traditional approaches to modern methods.

In 1973, the first **gene therapy** trial involving human subject was carried out. The patients of two sisters suffered from dementia caused by the deficiency of a rare enzyme. An American scientist and several German doctors were in charge of this test. The second gene therapy trial was conducted years later in 1980 in the United States, intended to treat two patients with severe thalassemia. But the results were unsatisfactory. Until the early 1980s, W. French Anderson outlined the principle and perspective of gene therapy. Many scientists experimented intensive tests of gene transfer and gene labeling protocols in animal models, and eventually made

significant breakthroughs for the theoretical and practical solutions of gene therapy. Joyner and his colleagues first successfully transferred a neomycin phosphotransferase (NPT) gene from the bacteria into hematopoietic stem cells using a **retrovirus vector**. In fact, the successful gene therapy was performed by Anderson and others in 1991 on two girls with severe combined immunodeficiency (“bubble-boy” syndrome).

In 1976, Walter Gilbert and Frederick Sanger worked out methods on DNA sequencing, called **Maxam-Gilbert method** and **Sanger chain-termination method**, respectively. In 1977, scientists employed recombinant DNA technology to generate recombinant peptide chains of the human **insulin**, and then produced the protein products in *E. coli*. Thus, the first protein drug by genetic engineering was invented, and this marked the beginning of a new era of drug production.

In 1980, scientists Botstein, White, Skolnick and Davis took the responsibility to design the framework of the mapping of the entire human genome. Theoretically, this diagram allows any single base mutation in the human body to be identified by simple two steps. In 1986, American biologist Nobel prize laureate Dr. Dulbecco proposed to study the human genome by sequencing the complete sequences with the full genetic information. In 1987, the US Department of Energy (DOE) and the National Institute of Health (NIH) started conjointly to work on the **Human Genome Project (HGP)**, and later officially initiated in 1990. The main objective of this project was to complete the sequencing work of all 3×10^9 bp sequences of a human, map the exact location of all genes, and acquire various information regarding the structure, function and expression regulation, disease mutations of genes.

In 1991, in the first international conference of gene mapping, **transgenic animal** models were recognized as the fourth generation technology, following linkage analysis, somatic cytogenetics and gene cloning. This became one of the important turning points along the history of biology for its development. In 1997, Ian Wilmut cloned sheep “Dolly” from adult sheep udder cells.

1.3 Basic Content of Molecular Biology

The molecules inferred in the molecular biology mainly stand for the large biomolecules of proteins and nucleic

acids. The studies of the structure and functions of these molecules are purposed to reveal the nature of biological phenomena, which inevitably related to genes. Molecular biology not only focuses on the structure of individual genes, but also interests in the interconnection and interaction of various large biomolecules centered with the gene functions. As we know that stimulation signals outside cells are able to regulate the gene expression through the series interactions involving sets of molecules. The expression of the gene products in return also influences the gene structure and function, thus to impact biological processes. How these interactions and regulation are achieved and maintained in lives is the central question the molecular biology needs to answer. As various molecular biology technologies and the understanding of gene biology rapidly progress, including the power of DNA recombination, scientists now are able to precisely dissect the gene structures, and can further manipulate the genes artificially as well.

The current molecular biology includes not only the key factors of structure and function, but also the aspects about information. It focuses on the structure of the important biological molecules, and tries to address the structural questions via the functional studies on how these molecules perform in cell metabolism and what biological information these molecules are carrying or delivering. Physical methods and the methods in structure chemistry, bioinformatics, and computational biology are frequently used for molecular modeling and resolving protein spatial structures. Such information is extremely helpful to understand the interactions between large biological molecules among themselves, or with small molecules like the metabolites or drugs.

The major historical, as well as the future, aspect of studies in molecular biology taught in medical college will still and continues to be the **structural biology** of large biological molecules of important functions; the **expression and regulation of genes**; the **regulation and homeostasis maintenance** of metabolic processes; the **development of organisms**; and **molecular medicine**. Along with the development of molecular biology, the DNA recombination technology has been serving as an important driving force that enabled the researcher to manipulate the living organisms at demand with ease. Currently, as more and more genes were characterized by their functions, the integrated and holistic understanding of the interaction network of the genes and their products is

greatly facilitated with the emerging technologies of bioinformatics and metabolomics. With the further development of such related fields, molecular biology as a well established science will enter to a new level and continue to play important roles in medical sciences.

1.4 Role of Molecular Biology in Medical Science

Molecular biology is a science with young history, and yet is closely related to nearly every branch of life sciences. Its principles and techniques are adopted by many disciplines of biomedical sciences, and greatly promoted their progress and development. As a result, the biological science as a whole has reached a new level. On the other hand, the development of molecular biology is also greatly supported by many other disciplines with a great variety of applications, especially regarding to each individual gene with its specific functions. Molecular biology itself is also branched into several subcategories.

As medicine is one of the most important areas in life sciences, it is influenced by the theories and technologies to a great extent. So-called **molecular medicine** becomes an independent research field, as well as a subject with importance of medical applications. It focuses on the studies of genes that related to the growth, development, disease, aging and even death of human beings. In many occasions, the research also involves the use of animal disease models.

Although each of the branched disciplines of medical research has their own objective, subject and focus, the medical research as a whole have common interests in the five aspects of physiology, pathology, prevention, diagnosis and treatment. Molecular biology revolutionized these research fields to the gene (i. e., molecular) level, therefore molecule physiology, molecule pathology and molecular pharmacology, molecule microbiology, molecular immunology, as well as molecular internal medicine and molecule surgical medicine etc., all have emerged in the era of modern molecular biology. The molecular biology itself has also branched out a medical molecular biology for the special interest in the research of medical sciences. Medical biology mainly concentrates on the structure and function of disease related genes, and regulation of their expression. It also explores the potential of the genetic engineering of these genes, and applications for gene diagnosis

and gene therapy. Currently the progress in medical molecular biology serves as a driving force for the development of medical science in each specific field.

From the following examples, we may easily appreciate the indispensable role of molecular biology in the research of modern medical sciences.

1.4.1 Cancer Research

Represented by the discovery of **oncogenes**, the cancer related research has made important breakthroughs owing to the development of molecular biology. This helped the gradual clarification about the causation of various cancers, which was impossible without molecular biology technologies. The results revealed that the abnormal expression and activation of oncogenes appeared to be one of the major causes of **tumorigenesis**. In fact, the natures of oncogenes are cellular housekeeping genes of crucial functions, called the **proto-oncogenes**. What are the functions of these genes; how are they regulated; what are the exact mechanisms for their abnormal expression; why the abnormal oncogenes lead to carcinogenesis; and are there any anti-cancer interventions can be performed that targeted to the abnormal oncogenes? All those questions have been and still remain to be the important issues of molecular biology. As more cancer-related genes are discovered, especially after their interactions are better understood, the physiological and pathological functions of proto-oncogenes will be much clear. Some of the findings will be guiding or directly used for the cancer therapies. For example, cancer cells are weak for antigenicity, and they produce immune suppressing factors. As a result, cancers often escape from immunity surveillance and smother the immune responses. With medical molecular biology techniques, progress has been made to overcome this problem. The lymphokine genes were introduced into cancer cells to increase their antigenicity and reduce their suppression of the immunity. This strategy has been started in the test of clinical trials.

1.4.2 Study of Genetic Diseases

To date, the numbers of identified **Mendelian genetic diseases** in humans exceeded 500 different kinds. As the knowledge and technology of molecular biology rapidly developed, the research in the pathology, diagnosis and therapy of genetic diseases has advanced significantly. Many genes of the disease allele have been isolated, and the causal genetic defects, such