Preface

I started my career with theoretical population genetics in the 1960s after a short period of field work experience concerning quantitative genetics. At that time evolutionary studies were conducted primarily by comparing phenotypic characters among individuals within and between species. These studies did not give clear insights into the cause and the effect of evolution, because the genetic basis of phenotypic characters was not well understood.

In theoretical population genetics, we could consider a set of alleles at one or a few loci and study the theoretical changes of genotype frequencies due to mutation, natural selection, and genetic drift. These studies gave only possible evolutionary changes of populations, but they were still much better than intuitive arguments. For this reason, a large body of mathematical theories of evolution was developed. These theories depended on many simplifying assumptions about the breeding system, population structure, selection coefficients, gene interaction, etc., and different assumptions about these factors often generated very different predictions of evolutionary changes. This resulted in many controversies which could not be resolved easily because of the difficulty of doing experimental studies. At that time, population genetics was dominated by neo-Darwinism with the idea of pervasive natural selection, and I was working within the framework of neo-Darwinism. Furthermore, because it was difficult to identify the homologous genes between different species, population genetics studies were primarily concerned with the gene frequency changes within species.

In the early 1960s a number of molecular biologists were working on the evolutionary changes of genes and proteins at the molecular level, and this approach of studying evolution was integrated with population genetics theory in the latter half of the 1960s and in the 1970s. This integration transformed the study of evolution profoundly. First, we could now identify homologous genes in different species and study long-term evolution of genes by comparing the nucleotide or amino acid sequences from different species. Second, molecular data on the evolutionary change of genes soon indicated the importance of mutation in evolution. Third, comparison of the DNA contents of different species suggested that gene or genome duplication occurred frequently in the process of evolution. Because gene or genome duplication is a form of mutation in the broad sense, I realized that mutation is the driving force of evolution. Yet, this view was regarded as a heresy at the time when neo-Darwinism dominated the field. In the meantime the neutral theory of molecular evolution was proposed to explain the evolution of genes and proteins. This theory clearly showed that the evolution of nucleotide sequences has occurred mainly by random fixation of neutral mutations. However, most neo-Darwinians did not pay much attention to this discovery, because they believed that neutral evolution has nothing to do with phenotypic evolution, in which most evolutionists are interested. In fact, even the proponents of the neutral theory of molecular evolution stated that phenotypic evolution occurs mostly by natural selection, as will be mentioned later.

By the early 1970s, I came to believe that the principle of phenotypic evolution must be the same as that of molecular evolution because both types of evolution are controlled by mutation at the DNA level. I briefly presented this idea in my 1975 book *Molecular Population Genetics and Evolution*. However, few people paid attention to this view. I elaborated this idea in several publications in the 1980s including my 1987 book *Molecular Evolutionary Genetics*, but the response was not great. The problem was that the molecular biology of morphogenesis was not well developed at that time and it was not easy to show the roles of mutation in phenotypic evolution convincingly.

In the past two or three decades, this situation has changed dramatically, and it is now possible to evaluate the roles of mutation and selection in phenotypic evolution at the molecular level. In the 1980s I became interested in understanding the evolution of the adaptive immune system of vertebrates by studying evolutionary changes of immunoglobulins, major histocompatibility complex genes, T-cell receptor genes, etc. In later years I also studied the evolution of genes controlling body segmentation (HOX genes), flowering in plants (MADS-box genes), sensory receptors, microRNAs, etc. in collaboration with graduate students and postdoctorals in my laboratory. These studies have been very helpful in clarifying my view that the driving force of evolution is mutation and natural selection is of secondary importance. This view is different from Hugo de Vries's mutation theory, and I previously called it the new mutation theory of evolution or neomutationism. In this book, it will be called the theory of mutation-driven evolution to convey the message that the importance of natural selection is duly appreciated in conjunction with the role of mutation.

During this period, I came to realize that evolutionary biology must be rebuilt upon the knowledge of molecular biology. Every biological process involved in metabolism and reproduction of organisms is governed by the function of DNAs and RNAs at the most fundamental level. Environmental effects on the formation of organisms can also be studied by using the knowledge of epigenetics. Natural selection and genetic drift are ultimately determined by the differential rates of birth and death of individuals, which are again the consequences of metabolism and reproduction. Population genetics and ecology are useful for visualizing the long-term change in populations and for understanding the consequences of population size change and competition and cooperation of organisms. However, the prediction of population genetics is always abstract, and it does not give any explanations about how a particular character such as mammalian sex determination or vertebrate brain has evolved. To answer these types of question, we must use the molecular biology approach. For this reason, I have become interested in explaining the evolution of specific characters and attempted to give molecular answers to some of the questions Charles Darwin and other investigators have posed in the past.

Evolution is a broad subject encompassing many areas of biology such as molecular biology, genetics, ecology, sociobiology, and paleontology. In this book, however, I will be concerned primarily with the mechanism of evolution with an emphasis on genetic and molecular aspects. I have decided to do this, because this is the backbone of evolutionary biology and it has been controversial ever since Darwin's publication of *Origin of Species*. I will discuss this problem with a historical perspective to understand various theories of evolution presented in the past 150 years and their relationships with the new theory of mutation-driven evolution. The historical perspective presented here may not necessarily be the same as that of currently popular books such as Mayr's *Growth of Biological Thoughts*, because I found some misconceptions in these books when I examined the original sources. I have tried to present the views of the original authors as much as possible.

However, the main purpose of this book is to present a comprehensive theory of mutation-driven evolution considering the latest information on molecular and phenotypic evolution. We are all aware that phenotypic characters show an enormous amount of variation both within and between species. All this variation is ultimately caused by differences in the structure and function of DNAs and RNAs, whether the characters are affected by environmental factors or not. Therefore, phenotypic evolution must be ultimately explained in terms of molecular biology. For this reason, I will consider the evolutionary change of molecules, genes, and genomes and then the molecular basis of phenotypic evolution. Of course, our knowledge of the molecular basis of phenotypic evolution is quite limited. We have little idea about how the human brain, the elephant's trunk, the body structures of whales, etc. have evolved. Nevertheless, we are beginning to understand the molecular basis of many complex phenotypic characters, and the future of the study of phenotypic evolution is bright. However, these problems have to be studied by using new technologies and new evolutionary concepts.

In this book, I have tried to cover these new developments in evolutionary biology and critically examine both old and recent findings to establish the general principles of evolution. In my view evolution is not the enhancement of fitness of individuals or populations, but it represents the increase (or decrease) of phenotypic complexity, which may be measured by the number of cell types or some other quantity. For this reason, my conception of evolutionary biology is different from the currently popular views. In this book, I hope I have explained the theory of mutation-driven evolution in a logical fashion.

This book is written as a monograph rather than a textbook. Therefore, the topics covered are not necessarily comprehensive, and it is assumed that the readers are acquainted with the basic knowledge of genetics and molecular biology. Nevertheless, I have presented essential aspects of these disciplines that are required for understanding my arguments. I have used many examples to illustrate the importance of mutation in evolution, and in this case I have often presented the studies which have been conducted in my laboratory. I have done this because I am familiar with them and therefore I can avoid serious errors. However, this book is based on the knowledge accumulated by numerous investigators over the past several decades though the sources are not always clearly mentioned.

In Chapter 1 a brief history of scientific studies of evolution is presented, starting with Charles Darwin's work on evolution and covering subsequent development of studies that have led to the idea of mutation-driven evolution. Chapters 2 and 3 are devoted to the development of neo-Darwinism and its significance and limitations for the study of evolution. Chapters 4 and 5 present evolutionary changes in genes and genomic structures and their relationships with phenotypic evolution. The molecular basis of phenotypic evolution is presented in Chapter 6 with an emphasis on the mechanism of gene expression in the development of phenotypic characters and the interaction between genes and environmental factors. In Chapter 7 various mechanisms of generating hybrid sterility and inviability are discussed in relation to the formation of new species at both genic and genomic level. Here a new view of speciation is presented. Chapter 8 is devoted to the evolution of several important phenotypic characters such as sex determination and insect caste systems. Chapter 9 presents the general concept of mutation-driven evolution and its significance in the study of evolution. The final chapter presents a general summary of this book and conclusions.

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Masatoshi Nei
Pennsylvania State University