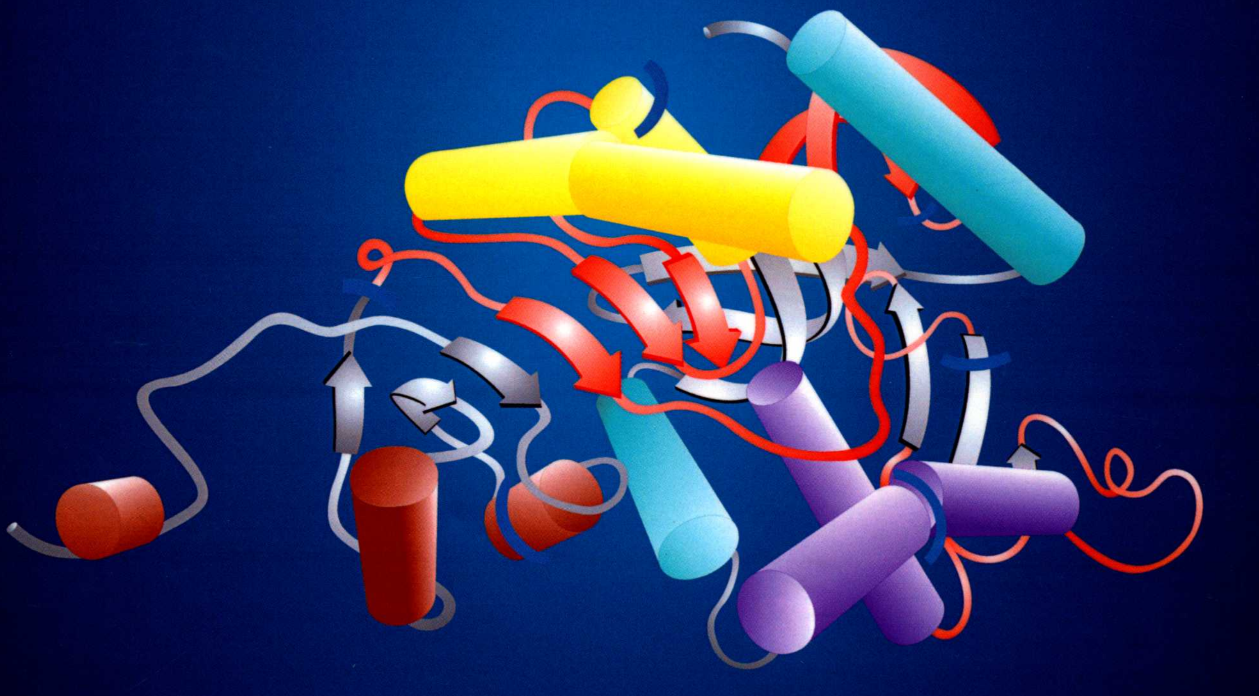
MEDICAL BIOCHEMISTRY



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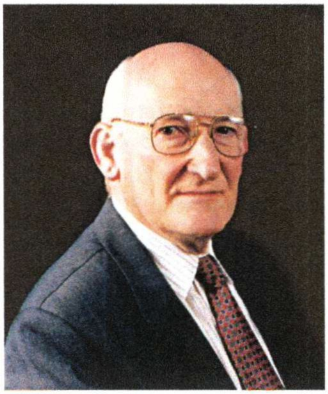

Dr. A. Blanco obtained his MD and PhD (in Medicine) degrees in the Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina (UNC). During all his academic career, he worked in the Department of Biochemistry of that university, moving up in the ranks from Instructor, Assistant, Associate, and Full Professor to becoming Chairman of the department. He remained as Chairman at the UNC from 1965 to 1996, the year in which he retired. He was then named Emeritus Professor. Between 1961 and 1965, he obtained support from the National Institutes of Health to work as a Research Associate in the Johns Hopkins University Medical School in Baltimore, MD, USA. From 1971 to 2001, he was Researcher of the National Council of Scientific Investigations of Argentina in the highest category. He is currently a member of the National Academies of Sciences and of Natural and Physical Sciences, and of the Academy of Medicine of Córdoba, all from Argentina. He has published 5 textbooks for medical students and 126 original research articles in international journals. He has received numerous awards and distinctions for his research and teaching activities.

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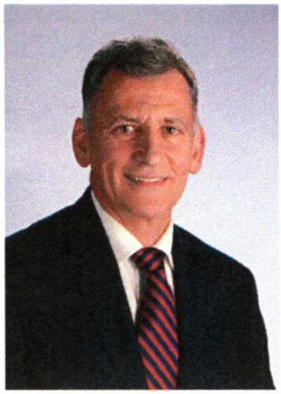

Dr. G. Blanco obtained his MD and PhD (in Medicine) degrees in the Faculty of Medical Sciences, National University of Córdoba, Córdoba, Argentina (UNC). As a Fellow of the National Council of Scientific Investigations of Argentina, he completed his Doctoral Thesis dissertation, which received the Award of the UNC. He was Instructor in the Department of Biochemistry of the UNC from 1986 to 1990. Between 1990 and 1995, he performed his postdoctoral training, working as a Research Associate in Washington University School of Medicine in Saint Louis, MO, USA. In 2001, he was appointed Assistant Professor in the Department of Molecular and Integrative Physiology in University of Kansas Medical Center in Kansas City, KS, USA. He moved through the ranks as Associate Professor and Professor, and at present he serves as the Kathleen M. Osborn Chairman of the department. Dr. G. Blanco has published more than 60 original research articles in international journals. On account of his scientific investigations and teaching activities he has received numerous awards and distinctions.

Preface

This is the English version of the 10th Spanish edition of *Química Biológica*, published by El Ateneo, Buenos Aires, Argentina.

The book is primarily intended for premedical and medical students. It presents a comprehensive and updated view of the biochemical processes that occur in the human body in health and disease.

Preparing a Biochemistry textbook for students being interested in the medical field poses a great challenge. This requires the selection, from the enormous amount of information available, of the data that will be most relevant to the future physician; the presentation and discussion of the material in a didactic manner to facilitate the learning process; and an up-to-date revision of the topics that include the most important discoveries resulting from the rapid progress in the Biological Sciences and Biochemistry areas.

Following the experience that we have acquired by teaching biochemistry for medical students over the years, our approach to this book was to start describing elemental biochemical concepts, continue developing each topic incorporating more complex concepts and new discoveries with sound experimental basis, widely accepted by the scientific community, and emphasizing their relevance to different clinical scenarios.

Our purpose with this textbook has been to offer a useful tool that will help students learn the bases of Biochemistry and that will serve as a reference for more advanced biochemical concepts, which will cover the needs of the future professionals working in the health care area.

We hope that the textbook will also spark in the reader, their curiosity and interest for scientific research, which will help to continue expanding the frontiers of knowledge.

Introduction

Biological Chemistry, the science that seeks to understand life processes at the molecular level, comprises two broad areas: one studies the components of living organisms and is called *Static* or *Descriptive Biochemistry*; the other investigates the chemical transformations that occur in biological systems and is known as *Dynamic Biochemistry*. Both of these areas have witnessed an amazing development in the past years.

Descriptive Biochemistry. Due to the vast complexity of living organisms, studying the composition of living beings has been an extremely challenging undertaking that demands immense research efforts. Even the simplest unicellular organism contains a myriad of substances.

The study of the components of cells and tissues requires isolation, purification, structure determination, and characterization of their functional properties. Initially, biochemists directed their attention to simple compounds, which could be readily removed from animal or plant organisms, or compounds that could be easily obtained by degradation of more complex substances.

As in other disciplines, the advancement of Biological Chemistry has closely followed technological developments. The availability of new equipment and methods with increasing sensitivity and resolution has allowed researchers to study molecules of the highest complex organization. Isolation, purification, and analysis of macromolecules (proteins, nucleic acids, and polysaccharides), which were once unimaginable, have now become customary in biochemical laboratories.

The discovery of the structure of biological molecules has advanced the understanding of their functions and mechanisms of action, and has helped deciphering their roles.

Dynamic Biochemistry. Countless chemical reactions continuously take place in living organisms in what is known as *metabolism*. The study of these reactions is contemplated by dynamic biochemistry. The earliest goals in this area of biochemistry were directed to decipher the changes that occur to substances ingested with the diet and to identify the origin of waste products excreted by the body. Later, studies were focused to understand the biosynthesis of different endogenous components of the body.

The advances made in the area of metabolism have been, in part, a consequence of the progress of *enzymology*. The study of enzymes, catalysts of biochemical reactions, has been crucial in the interpretation of biological phenomena.

Most chemical conversions in living beings take place gradually, through a series of reactions or *metabolic pathways* which, through sequential steps, convert a compound into a final given product.

From the first observations in the second half of the 19th century, researchers have worked relentlessly to unravel the astounding diversity and complexity of chemical pathways. This resulted in the assembly of "metabolic maps," which illustrate the intricate pathways that compounds follow as they are chemically modified. Although these maps look like a chaotic network, each reaction proceeds in a highly ordered and coordinated manner. In a normal individual, metabolic reactions are exquisitely adapted to serve the needs of each cell and the organism as a whole. Studies on the regulation and cross talk between metabolic pathways have been particularly active in the last 60 years. These have uncovered numerous highly refined regulatory mechanisms which, through modulation of enzyme activity, precisely coordinate the ordered "traffic" of substances, to adjust the flow of compounds along specific metabolic pathways as required.

The nervous and endocrine systems play an essential role in coordinating and integrating the function of many pathways in multicellular organisms. These systems operate in response to a variety of stimuli by releasing intermediary substances or chemical messengers. These messengers include neurotransmitters, hormones, cytokines, and other factors that selectively target receptors to trigger signal transduction mechanisms, which will finally induce specific cell effects. Signal transduction mechanisms have been shown to exhibit a striking degree of complexity, displaying a series of mediator molecules that interact in different ways to activate or inhibit particular events in the cell.

The unity of the biological world. Despite their great diversity, living beings show a remarkable unity with respect to the structure and basic processes that govern their function. For example, although macromolecules, such as proteins and nucleic acids, differ from species to species, and even from individual to individual, they show an overall basic structure which follows the same general plan. All proteins are composed of long chains of the same 20 fundamental units (amino acids), and nucleic acids are constituted by long strands resulting from the assembly of 4 basic structures (nucleotides).

Likewise, the mechanisms underlying cell metabolism also show great similarity even across phylogenetically distant species. For example, the reactions by which human skeletal muscle fibers obtain energy for contraction mimic the transformations that yeast and other microorganisms perform during the process of fermentation. This unity in biology has allowed studying simpler organisms as an approach to understand the function of multicellular organisms of higher complexity.

The body as an energy converting machine. According to their energy requirements, living beings can be divided into *autotrophic* and *heterotrophic*. Plants are autotrophic, which means they are able to synthesize complex organic compounds (carbohydrates, fats, nucleic acids, and proteins) starting from simple inorganic substances (water, carbon dioxide, nitrogen, and phosphates). The energy for this synthesis comes from the sun (*photoautotrophs*) or from electron donors provided by inorganic chemical sources, such as ammonium, sulfur, and ferrous iron (*chemoautotrophs*).

In contrast, multicellular animals are heterotrophic, depending on the intake of compounds produced by other organisms. Normally, carbohydrates, lipids, proteins, vitamins, and minerals that animals obtain from the diet undergo chemical changes that serve two main purposes: (1) the transfer of the energy contained in these substances and (2) the supply of raw materials for synthesis of the organism's own molecules. This process of synthesis, like other cellular activities, requires energy.

The chemical energy obtained from components of the diet can be transformed to fuel the multiple activities occurring within cells. For this reason, living organisms can be considered true energy converting machines. Chemical reactions called *exergonic*, which are those accompanied by the release of energy, are frequently coupled with others that require energy (*endergonic*). Many of these reactions result in the production of new molecules that are able to trap and store the released energy until it is needed. Among the many molecules that play this role, *adenosine triphosphate* (*ATP*) is the most common carrier of readily usable chemical energy.

Reproduction capacity. A distinctive property of living beings is their ability to reproduce and create, over generations, new organisms that are similar to their predecessors in external features, internal structure, and physiological characteristics. This is possible through the transmission of heritable traits, from cell to cell and from parents to offspring, carried in the *genetic information* contained in deoxyribonucleic acid (DNA) found in chromosomes. This genetic information is ultimately expressed through the synthesis of proteins with unique characteristics for each species and individual. The "code" or "language" of the genetic information in DNA is universal and practically the same for all living beings. This is another example of the remarkable unity of the biological world, which points to the common origin of Earth's living matter.

Changes (*mutations*) that spontaneously appeared in the "genetic message" through millions years of evolution have created the diversity of the living world that we see today, and have shaped the particular characteristics of each species.

The progress made in recent decades on understanding the structure and function of DNA has been remarkable. This has allowed a better understanding of the mechanisms responsible for the transmission of genetic characteristics and the eventual modifications seen between an individual and its progeny. In addition, the understanding of DNA has opened unforeseen opportunities for applications in different fields. A relatively recent discipline, *Molecular Biology*, which emerged within Biochemistry, has made astonishing contributions to our knowledge of the complete sequence of the DNA in the genome of humans, plants, and animals. Also, this discipline has allowed the manipulation of genes; a technology that has direct application in biology and medicine, including the production of genetically modified organisms with specific desired properties and the development of genetic therapeutic approaches directed to treat a variety of diseases.

Along with the evident benefits brought about by the advancement of molecular biology, new ethical and social challenges arose, which require careful consideration by scientists and the general public.

Scope of Biological Chemistry. Advances in Biological Chemistry have opened new horizons and prompted the development of other disciplines, such as Cell Biology. The expansion of Biochemistry into areas, such as Molecular Biology and Cell Biology, has made the boundaries between these disciplines less defined. At present, any Biological Chemistry textbook needs to expand its scope "invading" into areas which were originally foreign to it.

Reductionism–complexity. Scientific research has provided rational explanations for the properties and functions of biomolecules. Today, biochemistry has a solid experimental basis, which resulted from a reductionist conception in the study and interpretation of phenomena. This strategy has proven highly successful in acquiring new knowledge. From studies carried out in isolated molecules to those performed in reconstituted in vitro systems, scientists have been able to develop models in an attempt to describe different in vivo processes.

As these models developed, it became apparent that biological systems are highly complex. Paradoxically, achievements of reductionism have shown its limitations. It is now clear that living organisms cannot just be defined as the sum of their components. The integrated operation of these components generates a functional intricacy that makes the analysis and understanding of living beings extremely difficult. The vast complexity of biological phenomena represents a major challenge for the human mind. This challenge is the stimulus that fuels scientific curiosity, drives the continuous search for understanding biological phenomena, and contributes to the constant expansion of the frontiers of knowledge.

Importance of Biological Chemistry. Without a doubt, the progress of Biochemistry has been one of the factors that have contributed the most to the development of the Biological Sciences. Medical disciplines have benefited

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tremendously from the advances of Biochemistry, and it is anticipated that this progress will continue at an even faster pace in the future.

Biologists and physicians need to acquire a solid background in basic sciences. In Biological Chemistry, not only will they find the grounds for a rational interpretation of many physiological and pathological phenomena, but also the stimulus for a permanent search of new knowledge.

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