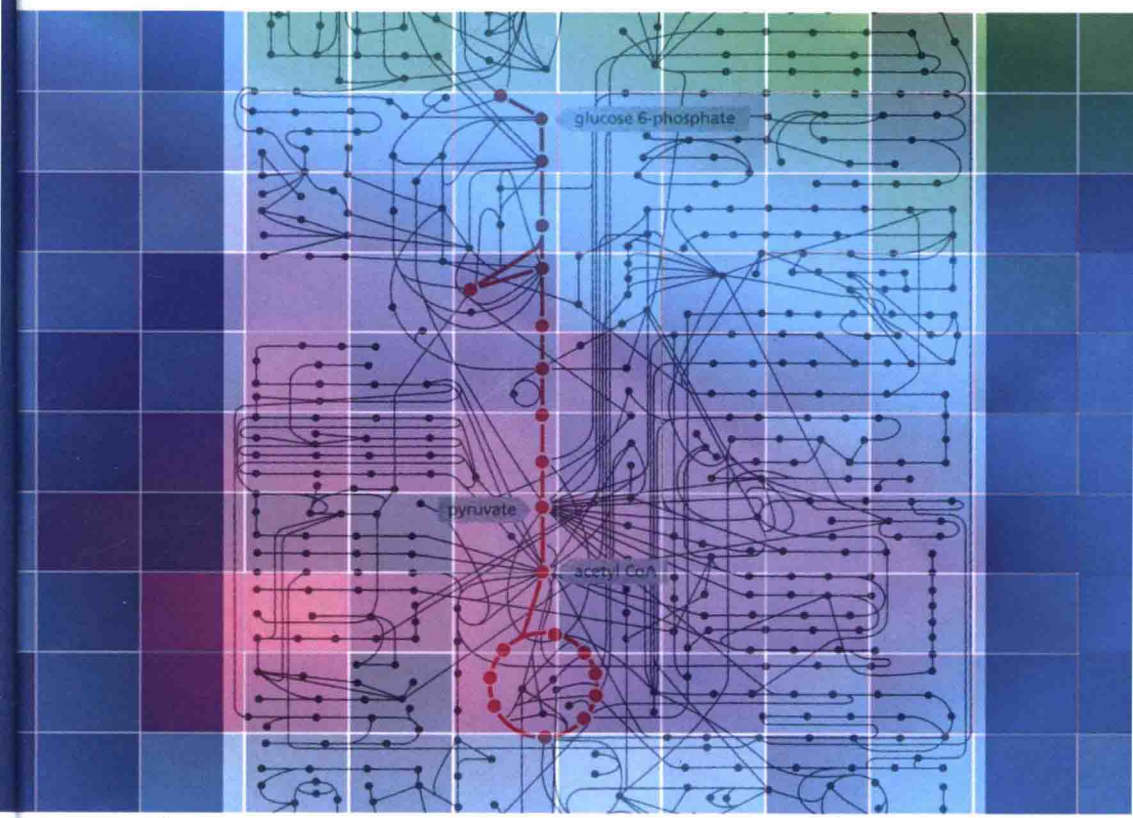
Metabolic Structure and Regulation

A Neoclassical Approach



Raymond S. Ochs

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NUTRITION

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There is a renewed interest in the fundamentals of energy metabolism, yet most people base their understanding on the views of generalists expressed in elementary textbooks. New techniques that enable analysis of thousands of metabolites provide useful data, but do not themselves substitute for an understanding of the fundamentals of metabolism. While classical ideas of metabolism are also valuable, some earlier ideas have not withstood further investigation. This book presents a personal philosophy but rests on what is broadly accepted by metabolic biochemists over the past few decades.

Some principles developed in this book include:

Kinetics – The kinetics of isolated enzymes is placed in a metabolic context. For example, the Km is a useful concept, but it can be misleading when considered as a means of interpreting enzyme inhibition, and it can be different yet in a pathway context.

The pathway view – This is a holistic perspective, in contrast to the reaction view, which is reductionist. For example, reaction cofactors such as NAD and ATP are connectors in the pathway view, but substrates or products in the reaction view.

Reversibility – Thermodynamics has been applied to metabolic pathways in earlier studies in ways that remain relevant today. This work rekindles the concept of near-equilibrium versus metabolically irreversible as separate classes of enzymes with distinct characteristics. A further type of reversibility emerges from the pathway view.

Signals and Pathway Flows – The richness of currently available information concerning signal molecules itself becomes a barrier to a broad understanding of function. This treatment considers just a few signal molecules: cyclic AMP, Ca^{2+}, AMP, and diacylglycerol, using balance and pathway considerations to place signaling in a metabolic context.

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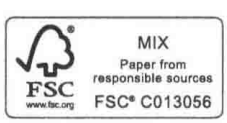

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To my wife Jessica for all her support, as always.

Introduction

There is new interest in metabolism [1]. Even the hard core molecular biologist James Watson recently said "I never thought, until about two months ago, I'd ever have to learn the Krebs cycle" [2].

In 1985, Richard Hanson predicted a return of investigators towards metabolism: "Students in the modern era regard metabolic pathways as a solved problem" [3]. He went on to predict a *metabolism redux*. Unfortunately, his prescience was off by about thirty years. Much of our information today comes from textbooks.

Yet metabolism is not a strong part of current biochemistry textbooks; the information is largely structural. Many of the ideas are handed down from earlier textbooks, and do not constitute a body of understanding that can be applied to the analysis of pathways.

The first and oldest pathway, glycolysis, has currency because of the Warburg effect: cancer cells generally have very high rates of glycolysis. Since most are aware that this pathway is relatively inefficient as an energy generator and yet cancer cells are surely survival specialists, it appears to make little sense. The Warburg effect dates from the early twentieth century; it is still under debate!

A paucity of systematic understanding of metabolism has led to a piecemeal approach, and some popular ideas that are not well founded. For example, many consider nicotinamide adenine dinucleotide (NAD) as a regulatory molecule, and adenosine triphosphate (ATP) as an energy barometer.

In this work, I present a metabolic viewpoint, mostly putting forth ideas that were at one time well established but at present not well known. The work is more holistic than reductionist, with the goal of establishing a set of principles as free as possible from contradiction. I name this construct *neoclassical* as it presents a largely orthodox view of metabolic ideas, which are valuable enough to be revived in the climate of a renewed interest and important advances in metabolic thinking as more investigators are becoming interested in the area.

One very popular idea that also has historical roots is the compartmentation[i] issue. This is advanced in different ways, but a popular thought is that pathway intermediates or ions can become concentrated within specific regions of a water space. This was recently hailed as a "hot area" in a cover story of metabolism and disease in *Cell* [4]. The discussants suggested that glycolysis enzymes were all bound together, just like the respiratory complexes. Overall, many view metabolism as a pile of old literature that seems to have nothing systematic apart from the connection diagrams that define pathways.

This notion is, in my view, unacceptable: it can explain anything. When concentrations don't change, it could be argued that they are in a local aqueous subspace that defies measurement. When they do change, it is not taken as a contradiction of compartmentation. No one investigating changes in mRNA levels would take data showing no change and argue that it must have changed but couldn't be measured because of localization. If the diffusion-defying hypothesis were really to be accepted, any hypothesis could be adopted. It would obviate an understanding of metabolic patterns, any use for equilibrium constants, or kinetic constants. We would also have

to discard the global metabolic measurements approach—metabolomics—which makes the assumption that in fact metabolites do equilibrate with the cell water. I will show that belief in compartmentation is nonetheless pervasive; eschewing the concept is essential if we are to attempt a consistent hypothesis.

In the following, I offer what Mandelbrot described in his monograph [5] as a personal essay rather than a cataloging of events. The first pathway is glycolysis, familiar to most, but the ideas presented may well be new, as the fundamental notions of a pathway, cofactors in general and ATP in particular are presented in a metabolic context. Next, a treatment of mitochondria is provided that, again, is fairly familiar territory, but also provides some distinct principles, one of which is importantly the distinction between isolated mitochondrial behavior and mitochondrial function in the context of an intact cell.

I next consider pathway connectivity, revisit compartmentation, and show how metabolism is more easily interpreted if we accept uniform distribution throughout the water space. I have also included some issues of stereochemistry as they apply to metabolism, and how to view transporters across membranes.

In the following chapter on enzymes, the presentation is orthodox from the standpoint of a kineticist, but unfamiliar if the reader's viewpoint is shaped by general textbook treatments. In particular, kinetic constants and enzyme inhibition analysis are presented in a way that assists interpretation of metabolic events.

Next, a focus on cell specialization puts pathways in context. Thus, a liver cell and a muscle cell have virtually identical pathways for energy formation; minor alterations in regulators or connected reactions account for their distinction. Following this are considerations of a few signaling systems. The distinctive treatment here is to consider signal systems as pathways as well, which leads us to unique viewpoints, in particular for that of calcium ions.

A separate chapter considers computers and metabolism. The discussion includes metabolomics as well as some earlier ideas that provide unique insight into metabolic problems. The combination of computing and various fields of scientific endeavor has invariably provided new outlooks, and metabolism is no exception.

The final chapter is a consideration of medical issues that are directly related to metabolism. This is not to say that genetic approaches are not crucial; James Watson overstated the case when he opined that genetics was not useful for solving key disease puzzles. What I hope to demonstrate in this work is that "learning the Krebs cycle" is not the solution. Rather, we need an introduction to a few basic principles of metabolism. A first step is to consider the metabolic approach as a systems view, which is taken in Chapter 1.

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ENDNOTE

i. This term is an unfortunate conglomerate, occasionally shortened to *compartment*, or lengthened to *compartmentalization*. Its meaning is also somewhat fluid, as it refers both to physical compartments in cells delimited by membranes, a definition which is universally accepted, and conceptual compartments in which different pools of metabolites exist in the same water space. As described in this treatise, the second type is at odds with known chemical description, and typically invoked to explain specific data anomalies.

Author

Raymond S. Ochs is a biochemist with a career-long specialty in metabolism spanning 30 years. Previously, he wrote the textbook *Biochemistry*, contributed the metabolism chapters to another text, *Principles of Biochemistry*, and co-edited a collection of articles published as *Metabolic Regulation*. His research interests concern major pathways of liver and muscle, including glycolysis, gluconeogenesis, ureogenesis, fatty acid metabolism, glycogen metabolism, and control by cAMP, Ca^{2+}, diacylglycerol, and AMPK. He is currently professor of pharmacy at St. John's University in New York, teaching biochemistry, physiology, and medicinal chemistry.

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