Understanding Human Metabolism

Does eating more carbohydrates, or fats, cause one to put on more weight? Are ketone bodies toxins or vital products that keep us alive during starvation? Does the concept of 'fat-burning exercise' hold true? In this game-changing book, Keith Frayn, an international expert in human metabolism and nutrition, dispels common misconceptions about human metabolism, explaining in everyday language the important metabolic processes that underlie all aspects of our daily lives. Illustrated throughout with clear diagrams of metabolic processes, Frayn describes the communication systems that enable our different organs and tissues to cooperate, for instance in providing fuel to our muscles when we exercise, and in preserving our tissues during fasting. He explores the impressive adaptability of human metabolism and discusses the metabolic disorders that can arise when metabolism 'goes wrong.' For anyone sceptical of information about diet and lifestyle, this concise book guides the reader through what metabolism really involves.

Keith Frayn is Emeritus Professor of Human Metabolism at the University of Oxford, UK. In a long and varied career studying human metabolism and nutrition, he has worked in various settings, from diabetes clinics to Accident and Emergency departments and Intensive Care wards. His work has been widely recognised with awards including the first Blaxter Medal of the Nutrition Society, the David Cuthbertson Lecture at the European Society of Parenteral and Enteral Nutrition, and Honorary Fellowship of the Nutrition Society.

The ***Understanding Life*** series is for anyone wanting an engaging and concise way into a key biological topic. Offering a multidisciplinary perspective, these accessible guides address common misconceptions and misunderstandings in a thoughtful way to help stimulate debate and encourage a more in-depth understanding. Written by leading thinkers in each field, these books are for anyone wanting an expert overview that will enable clearer thinking on each topic.

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Are you interested in your health and want to understand how your body functions? Do you want to learn the science behind how food and exercise interact and how together they can both foster wellbeing or lead to poor health and disease? This, and all you need to know about the key role of human metabolism for health and disease, is what *Understanding Human Metabolism* gives you. The author, Professor Keith Frayn, is probably the best teacher of human metabolism and nutrition of our times and has published several superb books on the topic for students of medicine and nutrition. This time, I would like to congratulate anyone without medical training but with an interest in human metabolism – this is *the* book for you.

Olle Ljungqvist, Professor of Surgery, Örebro University and Affiliated Professor of Surgery, Nutrition and Metabolism, Karolinska Institute, Sweden

Insightful, objective, easy reading. Nutritional biochemistry and metabolism in the right measure.

Teresa H M da Costa, Professor, Department of Nutrition, University of Brasília, Brazil

Everyone has a metabolism, and most people have a folk understanding of it. This very clear account of this actually complex subject brings science to bear on such understandings. Reading it will help you understand yourself better.

Stanley Ulijaszek, Professor of Human Ecology, University of Oxford, UK

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Foreword

Metabolism. A term that many people have heard of, but also one that very few would be able to define correctly. Among those who would be able to provide a definition, most would end up using terms from biochemistry such as glycolysis, Krebs cycle, and oxidative phosphorylation, remembering the hard time they had learning all these biochemical reactions and pathways at some point during their studies. This might make you wonder then if the concept of metabolism, and whatever it is about, has any relevance to your everyday life. Well, in this splendid book, Keith Frayn tells you that it does – and why it does. More than this, he explains to you what metabolism is, and that all these reactions and pathways are relevant to your everyday life. Understanding them will make you get a sense of what is going on inside our bodies when we eat food, as well as when we do not; why we may be fatter or thinner than we would have wanted to be; and why sugars and lipids are not bad for us but essential for our life. By describing research on these topics over several decades, Frayn also explains how we came to understand metabolism, and figure out many of the complex ways that our organs are interrelated and interdependent. Reading this book is a rewarding experience, as a lot that you have heard of will suddenly make sense. Frayn paints a beautiful picture that will help you understand why we eat what we eat, what happens to that once we eat it, and how our bodies have evolved to be able to adjust to what is available to eat. In today's societies in which food tends to be plentiful, this might sound irrelevant. Well, I would argue that exactly because food tends to be plentiful, understanding metabolism is crucial for being able to make appropriate and balanced choices regarding what to eat.

Kostas Kampourakis, Series Editor

Preface

Surely not another book about metabolism? I can almost hear it being said. There seems to be a plethora of books at present about how to prevent oneself becoming obese, how to lose weight if one has already become so, what one should eat, and especially what one should not eat. There are books about the importance, or otherwise, of exercise for maintaining weight and health, and books about how to live longer by eating the diet of our palaeolithic ancestors or our near-relations in the animal world.

But none of these really addresses the field that biochemists know as intermediary metabolism. That term refers to the chemical processes that occur within our bodies – mostly within our cells – that transform what we eat into useful energy, new bodily constituents, and waste products. Indeed, from a reading of current popular science on the topic of metabolism, you might well have the impression that 'metabolism' refers just to the 'burning' of foodstuffs with the result either of weight loss or weight gain. You would not then appreciate the myriad of chemical reactions that build up the substances of which we are made, break them down again when they are no longer needed, and create safely disposable waste products. Even our DNA, the material of which our genes is made, is formed from chemical building blocks that are the product of such reactions.

Many features of intermediary metabolism must have evolved a very long time ago, since they are common to all life forms – from bacteria to mammals (Chapter 1). But it seems natural for us to have a particular interest in our own metabolism – human metabolism. And there is good reason for that. What goes on inside us is a product not just of chemical reactions, but of a flow of information between different body parts regulating just what happens and

when – so that when I have just eaten a big meal, my cells begin to store nutrients, and when I have not eaten for some time, they will begin to release nutrients from these stores (Chapters 2 and 3). Such information flow, called metabolic regulation, is a product largely of our hormonal and nervous systems (Chapter 4).

If there is one feature of intermediary, or cellular, metabolism that is widely known it is perhaps the so-called Krebs cycle, more commonly called by scientists the citric acid cycle, discovered by Hans Krebs (later Professor Sir Hans Krebs). But even those who know the term may well not appreciate just what this assembly of chemical reactions does. It can be seen as the 'final common pathway' by which all nutrients are broken down, and linked to the release of energy in a form that can be used by cells for all the processes that require it (Chapter 5).

The really wonderful – and often not appreciated – feature of our metabolism is that it is active, and changing, all the time: when you eat breakfast after fasting overnight, metabolism changes quickly; when you start to exercise, it changes even more quickly. During a typical day, chemical reactions in our cells are being accelerated and slowed down in a highly coordinated manner, enabling us to continue leading our daily lives without giving this matter any thought whatsoever (Chapter 6). But I rather hope that, once you understand what these changes entail, you might think about them more than you probably do at present. Changes in metabolism, as just noted, are especially marked during exercise, when our muscles require a supply of energy, that may come from within the muscles' own cells, or may be brought in the blood from other tissues, especially our fat stores and our liver. However we measure 'metabolism', there is no doubt that it is going faster when we are exercising than when we are at rest. But the opposite is true in starvation. When the body is deprived of nutrients, then metabolism is suppressed, conserving the precious stores that we have of metabolic fuels. Our carbohydrate stores are especially precious, the proteins of which our bodies are mostly built even more so, and metabolic mechanisms come into play to preserve these for as long as possible whilst living off our usually plentiful fat stores. The way these changes are brought about in starvation and in exercise is a fascinating aspect of our metabolism that presumably evolved to allow our ancestors to chase, or run from, other animals, and to survive even when no food was forthcoming (Chapter 7).

There is a tendency nowadays to regard carbohydrates, fats, and proteins as separate entities which can each be considered in isolation. This cannot be the view of anyone who has seriously studied human metabolism. The metabolic fates of the three major energy-providing nutrients are, of necessity, intimately intertwined. Our bodies are all the time drawing upon individual nutrients for particular needs: indeed, each of our tissues has its own preferences for particular fuels at different times. And all these requirements must be coordinated. Metabolic scientists now understand many ways in which the metabolic fates of the nutrients inter-relate. At a very basic level, all energy-providing nutrients, including alcohol, feed into the same cellular mechanism for final disposal, the citric acid (or Krebs) cycle, mentioned earlier. They have to share this pathway, and, just like family members sharing a bathtub, they cannot all get in at once. In Chapter 8 we will look at the mechanisms that prevent overcrowding.

But of course, like any other finely tuned system, things can go wrong. Many diseases involve disturbances in one or more of the myriad of metabolic processes that keep us going. Some of these are inherited very directly from our parents. Others are the result of our environment, but most are a combination of both influences. There are fairly common examples of disorders in the metabolism of carbohydrates, fats, and proteins (or the amino acids that make up proteins), and there are more complex conditions that may involve all three, diabetes mellitus (commonly just called diabetes) being one of these. What is more, metabolic changes may underlie common diseases such as cardiovascular disease (e.g. heart attack, stroke) and even cancer (Chapter 9).

I consider myself very lucky to have been able to spend my career investigating something that I find so intensely interesting – human metabolism. About half-way through my career, I was tempted to write down my views of this field so I could 'spread the word'. The result was an undergraduate textbook, then called *Metabolic Regulation: A Human Perspective*. This book has proved to be popular for students and researchers in a variety of fields, and the current, fourth edition, is now called *Human Metabolism: A Regulatory Perspective* (written with R. D. Evans). But these books are not really 'popular science', as some reviews attest (e.g. *'Whoops! I requested this book not realising it was a textbook, I thought it would be a bit more (dare I say it?) dummed down. Not that I'm stupid, but this just isn't my field ….'*). So, this book, *Understanding Human Metabolism*, is now my attempt to

present some of the wonder of human metabolism to a wider audience. My aims are twofold. Firstly, I would like others to share my amazement at this wonderful system, the result of millions of years of evolution, and underpinning our daily lives. But, secondly, I really do believe that if more people were to understand just how their metabolism works, we might hear less of the simplistic views on diet and lifestyle that are so often peddled in the media.

Acknowledgements

I would like to thank the many people who encouraged me to study human metabolism, and worked with me during my long career, but they are too numerous to list here. I would, though, like to mention those who sparked my interest in metabolism during my undergraduate years in Cambridge, especially Nick Hales and Philip Tubbs. I was lucky to have such inspiring lecturers at a time when molecular biology was in the ascendency. I really learned how to do human metabolic physiology during my years with the Medical Research Council's Trauma Unit in Manchester, with the help of Manchester colleagues (I thank especially Rod Little), under the head of the unit, H. B. Stoner. A number of clinical colleagues helped me adapt to research work in an emergency setting, David Yates (the first Professor of Emergency Medicine in the UK) especially. During this time, George Alberti, Roy Taylor, and others at the University of Newcastle upon Tyne were very supportive with my metabolic work and helped me to become a better scientist. In Oxford, my 'boss' for six years was Derek Hockaday, who had built up a unit with wonderful facilities for human physiology, and I am grateful to him for allowing me to pursue my own developing interests in fat metabolism and nutrition. I worked with many, many colleagues in Oxford but especial thanks are due to Barbara Fielding, Geoff Gibbons, Leanne Hodson, Sandy Humphreys, and Fredrik Karpe, with each of whom I worked very closely for a long time. Intensive Care doctor Rhys Evans has been a good colleague and in recent years a co-author. My apologies to all those whose names I haven't been able to list.

The impetus to write this book specifically came from Anna Whiting at Cambridge University Press when I approached her with various woolly ideas

about writing something on metabolism. I am very grateful to Anna and her colleague Olivia Boult for steering me through the process, and to Kostas Kampourakis, the Series Editor, for his many insightful comments – in particular for his vigorous striking-out of any mention of 'purpose' in metabolism!

I am grateful to Fredrik Karpe and John Miller for sending me, and allowing me to use, data from the Oxford BioBank. Kiki Marinou read and helped me with the section on diabetic ketoacidosis, in which she has great clinical experience. Jenny Collins was happy for me to use ideas about 'metabolic channelling', discussed in Chapter 3, derived from her work with fat cells in my laboratory.

This is my first book aimed specifically at the non-scientist, and a number of people have helped me at various stages along the way by reading my drafts and steering me in the right direction, including my wife Theresa and my daughter Liz, and my friend Nick Havely of the University of York, an expert in fourteenth-century Italian, French, and English literature: a real test of my comprehensibility. I will dedicate this book, though, to my grandchildren, Rayya, Alastair, Jibreel, Daniel, and Laith, in the hope it may inspire them to an interest in science and medicine.