

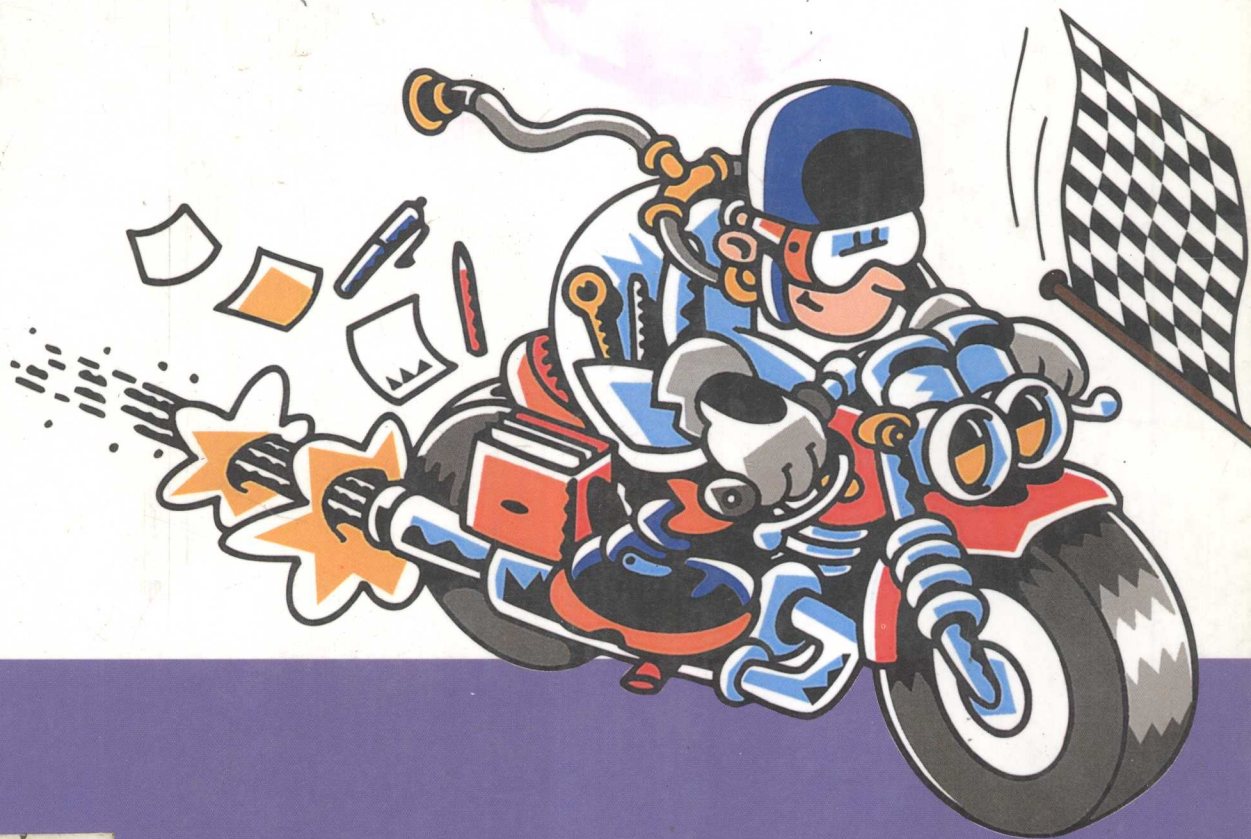
风暴式医学教程 *MOSBY'S CRASH COURSE* (原版英文医学教程)

代谢与营养

Metabolism and Nutrition

Sarah Benyon

with Daniel Horton-Szar as Series Editor



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(原版英文医学教程)

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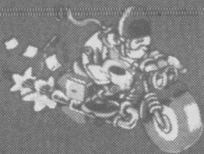
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Preface

Students have been known to pale at the mere mention of glycolysis; some have even passed out at the thought of the TCA cycle. Hopefully, this will no longer be the case.

This book has been written with a user-friendly approach using short blocks of text and simple, reproducible diagrams.

In Part I, I have set out the basic principles of metabolism and nutrition in order to cover the information necessary to pass the appropriate pre-clinical examinations in this subject. Chapter 1 serves as a guide on how to use this book and how to approach revision in the easiest way.

As a medical student, it is often all too easy, given the amount that has to be learned for examinations, not to question the reason behind learning something. In response to this, I have emphasized the relevance to clinical practice throughout the book in the hope of presenting a more colourful, wider viewpoint of the subject. A brief clinical assessment section has been included in Part II, which contains helpful guides to taking a basic history examination, and details of useful tests.

Details of important metabolic and nutritional disorders are set out in Part III in a format that is useful for quick reference. These have been included to complement Part I and do not necessarily represent those disorders most often encountered in a clinical setting, as many metabolic disorders are in fact rare.

I conclude the book with a self-assessment section in which I have focused on those commonly asked examination topics. Finally, although as far as possible the book is a statement of known facts, I have tried not to oversimplify and, where there are areas of uncertainty, these have been pointed out.

Sarah Benyon



Preface

Medical education is rapidly changing. The British General Medical Council has recommended more integration of preclinical and clinical teaching.

The Crash Course series caters for the changing trends in medical curricula—the basic science titles include a clinical part which relates the content of the basic core material to clinical teaching. This book emphasises the clinical relevance of biochemistry—it will help the student retain aspects of biochemistry most important for learning clinical medicine

This text provides realistic help for students learning for examinations as they are conducted today. The reader may also be interested in looking at Crash Course *Endocrine and Reproductive Systems* which is complementary to this volume.

Crash Course is intended primarily for students. However, it will also be useful for lecturers and tutors as it provides an important insight into how students perceive today's teaching of biochemistry.

Marek H Dominiczak
Faculty Advisor

OK, no-one ever said medicine was going to be easy, but the thing is, there are very few parts of this enormous subject that are actually difficult to understand. The problem for most of us is the sheer volume of information that must be absorbed before each round of exams. It's not fun when time is getting short and you realize that: a) you really should have done a bit more work by now; and b) there are large gaps in your lecture notes that you meant to copy up but never quite got round to.

This series has been designed and written by senior medical students and doctors with recent experience of basic medical science exams. We've brought together all the information you need into compact, manageable volumes that integrate basic science with clinical skills. There is a consistent structure and layout across the series, and every title is checked for accuracy by senior faculty members from medical schools across the UK.

I hope this book makes things a little easier!

Danny Horton-Szar
Series Editor (Basic Medical Sciences)



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Finally, my greatest thanks to my long-suffering family who have always given me endless support, encouragement, and kindness and to whom I dedicate this book.

Figure Credits

Figures 4.21 and 11.13 adapted from *Clinical Chemistry 3e*, by Dr W. J. Marshall, Mosby, 1995



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PROCESSES OF METABOLISM AND NUTRITION

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1. Overview of Metabolism

USEFUL DEFINITIONS

Metabolism

Metabolism is an integrated set of chemical reactions occurring in the body that enable us to extract energy from the environment and use it to synthesize building blocks that are used to make essential proteins, carbohydrates and fats. Some fundamental points to remember about metabolism:

- Each reaction does not occur in isolation but provides a substrate for the next.
- In this way, pathways are built up in which the ultimate product of each pathway forms a substrate for others, producing a continuous process.
- Many people liken metabolism to a map, the 'metabolic map', in which the pathways are like roads with 'stop-off points' (intermediates) along the way.
- Some of the roads are one way, meaning you have to travel a long way round to form some intermediates.
- Remember, when you make any journey, it is important to know where you are going but you do not need to know the names of all the places you travel through.

Metabolic pathways can be classified as either catabolic or anabolic.

Catabolism

Catabolism is the breakdown (degradation) of energy-rich complex molecules such as protein, carbohydrate, and fat to simpler ones, for example, CO_2 , H_2O and NH_3 . The energy released is 'captured' as adenosine triphosphate (ATP) and stored for use in synthetic, anabolic reactions.

Anabolism

Anabolism is the synthesis of complex molecules from simpler ones, for example, proteins from amino acids and glycogen from glucose. Synthetic reactions require energy which comes from the hydrolysis of ATP. Some examples of catabolic and anabolic pathways are shown in Fig. 1.1.

Examples of catabolic and anabolic pathways

Catabolic pathways names end in 'lysis' meaning 'to break down'	Anabolic pathways names end in 'genesis' meaning 'to create'
glycogenolysis: glycogen breakdown proteolysis: protein breakdown lipolysis: fatty acid breakdown glycolysis: glucose breakdown	glycogenesis: glycogen synthesis protein synthesis lipogenesis: fatty acid synthesis gluconeogenesis: glucose synthesis

Fig. 1.1 Examples of catabolic and anabolic pathways.



Although sometimes difficult to realize, all metabolic pathways do have a purpose and were not just invented in an attempt to make the first year at medical school very dull! Do not get 'bogged down' remembering every single step and enzyme in a pathway, you will not be asked to regurgitate this sort of information in an exam. It is much more likely that you will have to discuss the overall functions of a cycle and in which tissues they are particularly important.



The best way to revise metabolism is to take a large piece of paper (A3 size) and draw simplified cycles of all the pathways; listing the six key criteria in Fig. 1.2 for each: purpose/function, location, site, reaction sequence, key steps; and effect of inhibition.



Key criteria for remembering a metabolic pathway

Key criteria	Example—glycolysis
What is the purpose of the pathway? form a working definition of its function knowing: the substrates and products involved and any other key intermediates produced, for example, ATP or NADH	oxidation of glucose (substrate) to pyruvate (product) with the generation of energy in the form of ATP and NADH (the reduced form of nicotinamide adenine dinucleotide)
Location: particularly, tissues or cells in the body where the pathway is most important	glycolysis occurs in all cells of the body but in red blood cells it is the only energy-producing pathway
Site: where in the cell it occurs, for example cytosol, mitochondria or both	glycolysis occurs in the cell cytosol. pyruvate formed can be transported into mitochondria for addition by the TCA cycle
Sequence of events know the overall reaction sequence and the number of stages and reactions	glycolysis has 10 reactions
Pick out key steps: either those which form major control sites or those which are main 'branch points'	1. hexokinase reaction 2. phosphofructokinase reaction 3. pyruvate kinase
Effect of inhibition of the cycle	increase in [intermediates] which arise before the site of inhibition decrease in [intermediates] formed after the block

Fig. 1.2 Key criteria for remembering a metabolic pathway.

Regulation of pathways

Every metabolic pathway usually contains one reaction that is essentially irreversible and forms the 'rate-limiting' reaction of the pathway. Enzymes catalysing these reactions are subject to strict regulation to ensure that:

- The rate of the pathway is adapted to the cell's needs.
- For any molecule, its synthetic and breakdown pathways are not active at the same time as this would lead to a 'futile cycle'.

Most metabolic pathways occur in different cells and in different tissues of the body at the same time. The pathways must be carefully regulated, to ensure not only that the production of energy and intermediates is sufficient to meet the needs of the individual cell, but also to 'fit in' with the requirements of the rest of the cells in the body. The control of metabolic pathways must also be flexible enough to enable adaptation to

different environments, for example, fed state as opposed to starvation, or periods of exercise and so on. These control mechanisms must co-ordinate the pathways in all cells of the body.

Mechanisms of control

There are three main mechanisms of control of metabolic pathways; supply of substrate, allosteric control and hormonal control. Learn these now because they form the basis for control of all metabolic pathways.

Substrate supply

If the concentration of substrate is limiting, then the rate of the pathway decreases.

Allosteric control

Allosteric control may either be due to end-product inhibition, in which feedback inhibition by the amount of product may be positive (stimulate pathway) or negative (inhibit pathway), or to via the production of allosteric effectors which bind to regulatory sites on an enzyme that are distinct from the catalytic (active) site; they may increase or decrease enzymatic activity.

Hormonal control

There are two possible ways hormones such as insulin or glucagon can affect enzyme activity and thus the rate of metabolic pathways:

- Firstly by reversible phosphorylation of enzymes which may either increase or decrease their activity. For example, glucagon causes phosphorylation of both glycogen synthase and glycogen phosphorylase. Glycogen synthase is inhibited by phosphorylation whereas glycogen phosphorylase is activated. This



- Define catabolic and anabolic pathways (giving examples of each).

- What are the key points or criteria for learning metabolic pathways?
- Why are metabolic pathways regulated?
- What are the three main mechanisms of control?



ensures glycogen synthesis and breakdown are not active at the same time and is discussed fully in Chapter 2.

- Secondly, hormones can affect the rate of a metabolic pathway by induction; that is, they increase the amount of enzyme synthesized by stimulating the rate of transcription of its RNA. Similarly, under certain conditions hormones can inhibit transcription and thus the synthesis of certain enzymes—this is called repression.

BASIC PRINCIPLES OF BIOENERGETICS

Bioenergetics is the study of the energy changes accompanying biochemical reactions. It allows us to work out why some reactions occur (i.e. because they are energetically favourable) and why some do not. The direction and extent to which a chemical reaction occurs is determined by a combination of two factors:

- Enthalpy change, ΔH , which is the heat released or absorbed during a reaction.
- Entropy change, ΔS , a measure of the change in disorder or randomness in a reaction.

Neither enthalpy nor entropy change alone can predict whether a reaction can occur. Together they are used to calculate ΔG , the change in Gibb's free energy of a

reaction. It is ΔG that predicts favourability and direction of a reaction since:

$$\Delta G = \Delta H - T \times \Delta S$$

where T = absolute temperature in degrees Kelvin (K) ($^{\circ}\text{C} + 273$) and ΔG is the energy available to do work.

- If ΔG is negative, there is a net loss of energy during the reaction; making this a spontaneous, favourable, exergonic reaction.
- If ΔG is positive, there is a net gain of energy during the reaction and the reaction does not occur spontaneously; it is an endergonic reaction as energy must be added to the system to drive the reaction.
- If ΔG is 0, the reaction is at equilibrium. At equilibrium, the rate of the forward reaction is equal to the rate of the backward reaction and there is no net direction.

Be sure not to confuse exergonic and exothermic and endergonic and endothermic. Exothermic reactions release heat during a reaction and have a negative enthalpy change, $-\Delta H$. Similarly, endothermic reactions absorb heat during a reaction and have a positive enthalpy change, $+\Delta H$. However, it is not possible to predict favourability or direction of a reaction from enthalpy values. Remember only reactions with a negative ΔG occur spontaneously.



- What are the principles behind predicting the direction and extent of a reaction?
- Define exothermic, endothermic, exergonic, and endergonic reactions.



2. Carbohydrate and Energy Metabolism

GLYCOLYSIS AND ITS REGULATION

An overview of glycolysis

Working definition

Glycolysis is the sequence of 10 reactions that break down one molecule of glucose (a six-carbon ring) to two molecules of pyruvate (two chains of three carbon molecules) with the net generation of two molecules of ATP and NADH (the reduced form of nicotinamide adenine dinucleotide). Therefore glycolysis provides energy and intermediates for other metabolic pathways.

Location

All the cells of the body.

Site

Cell cytosol.

Aerobic and anaerobic respiration

Unlike other metabolic pathways, glycolysis can produce ATP under either aerobic or anaerobic conditions (see Fig. 2.2).

- Under aerobic conditions, the end-product, pyruvate, enters mitochondria where it is oxidized by the tricarboxylic acid (TCA) cycle and oxidative phosphorylation to CO_2 and H_2O with the production of large quantities of energy.
- Under anaerobic conditions, pyruvate is reduced by NADH to lactate in the cytosol. This allows the continued production of ATP in cells that lack mitochondria or are deprived of oxygen. This pathway produces only a small amount of energy.

Functions and importance of glycolysis

For many tissues glycolysis is an 'emergency' energy-producing pathway when oxygen is the limiting factor. It is of the utmost importance in:

- Red blood cells because they lack mitochondria and therefore glycolysis is their only energy-producing pathway.
- Active skeletal muscle when oxidative metabolism cannot keep up with increased energy demand.

- The brain because glucose is its main fuel (it uses about 120 g/day).

Glycolysis also contributes to the synthesis of certain specialized intermediates, for example, 2,3-bisphosphoglycerate, an allosteric effector of haemoglobin. It also helps in the metabolism of other sugars, especially fructose and galactose. (Both of these topics are covered later in this chapter.)

Glucose entry into cells

Glucose is not small enough to diffuse directly into the cell—it needs help. There are two transport mechanisms that exist specifically for glucose.

Facilitated diffusion

The first mechanism, facilitated diffusion, is mediated by a family of glucose transporters present in the cell membrane. At least five have been identified and are named glut-1 to glut-5; each has a different tissue distribution (Fig. 2.1). The transporters are integral membrane proteins that bind glucose and transport it through the cell membrane into the cell. Glucose enters the cell down its concentration gradient from an area of high concentration outside the cell to an area of low concentration inside.

Distribution of some of the glucose transporters		
Transporter	Location	Function
glut-1	most cell membranes	Provides basal glucose transport to cells at a relatively constant rate
glut-2	liver β cells of pancreas	Glut-2 transporters have a lower affinity for glucose than glut-1, therefore, glut-2 are only active when there is a high blood glucose, that is, in the fed state
glut-4	muscle and fat cells	Insulin dependent: muscle and fat cells 'store' glut-4 transporters in intracellular vesicles. In the presence of insulin, these vesicles fuse with the cell membrane resulting in an increase in the number of glut-4 transporters in membrane. Therefore insulin promotes glucose uptake by muscle and fat

Fig. 2.1 Distribution of some of the glucose transporters.



Sodium-glucose cotransporter

The second mechanism requires energy to transport glucose against its concentration gradient (i.e. from a low concentration outside the cell to a high concentration inside). This method of glucose transport occurs in the epithelial cells of the intestine (for the absorption of dietary glucose), renal tubules and the choroid plexus. The movement of glucose is coupled to the concentration gradient of sodium: sodium ions flow down their concentration gradient into the cell providing the energy to transport glucose into the cell against its gradient.

Trapping glucose in the cell

Glucose may enter the cell but will not necessarily stay there. Glucose must undergo irreversible phosphorylation to 'trap' it inside the cell. Why? Well, there are two reasons, first, phosphorylated glucose molecules cannot penetrate cell membranes because there are no carriers for them (glucose-6-phosphate is not a substrate for the glucose transporters). Secondly, converting glucose to glucose-6-phosphate keeps the concentration of free glucose inside the cell low compared with outside, maintaining the concentration gradient.

Stages of glycolysis

Glycolysis can be divided into two phases: an energy investment phase and an energy generating phase.

I Energy investment phase (reactions 1–5 in Fig. 2.2)

Glucose is phosphorylated and cleaved into two molecules of glyceraldehyde-3-phosphate. This process uses two moles of ATP to activate and to increase the energy content of the intermediates (see Figs 2.2 and 2.3).

II Energy generating phase (reactions 6–10)

Two molecules of glyceraldehyde-3-phosphate are converted into two molecules of pyruvate with the generation of four moles of ATP (see Figs 2.2 and 2.3). The overall reaction can be written as:

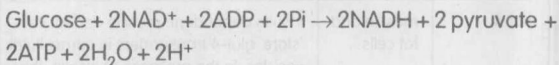


Fig. 2.2 The Embden–Meyerhof glycolytic pathway. Glycolysis takes place in the cell cytosol and consists of two distinct phases of energy investment (1–5) and energy generation (6–10). The names of the enzymes catalysing reactions 1 to 10 can be found in Fig. 2.3.

