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第二版

Metabolism & Nutrition

SECOND EDITION

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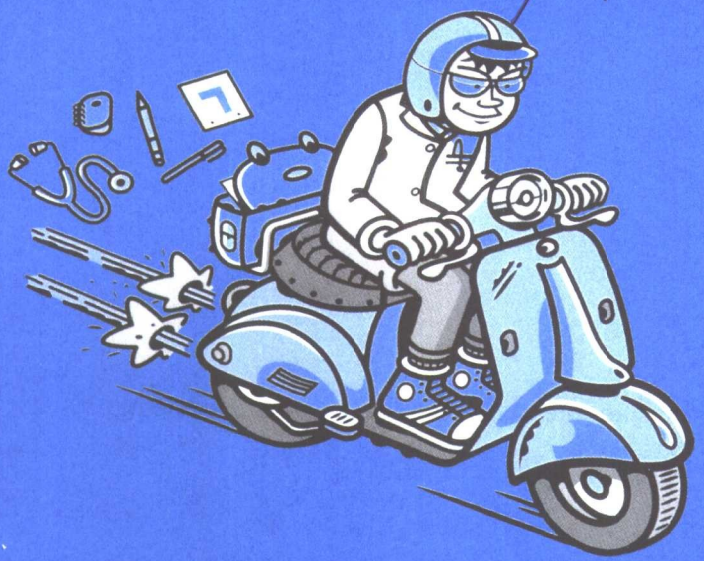

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Metabolism and Nutrition

SECOND EDITION

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Preface

It is an honour to be involved with a series that begins to appreciate the mind of the medical student.

The first edition of this book made the essentials of metabolism and nutrition accessible. Now this second edition fully integrates clinical relevance, hopefully encouraging you to really get to grips with the science. The assessment sections have been completely revised to test your ability to integrate information, apply metabolic theory to clinical practice and to ensure a good understanding of the underlying principles.

I have enjoyed putting this book together. I hope you enjoy using it!

Jason O'Neale Roach

The focus of the new generation of medical curricula is on providing integrated knowledge by breaking down artificial interdisciplinary barriers. Traditionally the most difficult barrier to break down was between the basic science and the clinical components of medical courses. This is a paradox, because it is precisely these two components that underpin the phenomenal progress in the understanding, diagnosis and treatment of disease made in recent decades.

New courses try hard to break this barrier. So do new books and this is where the *Crash Course* series comes in. The freshness of these books is in their pragmatism, their 'bottom-up' approach and their clinical relevance. Written by students, they focus on helping fellow students pass presently administered examinations.

Biochemistry advances very rapidly and so does clinical medicine. To address this, *Crash Course: Metabolism and Nutrition* homes in on areas that the authors, who have recently passed their exams, found important. But there is more to it: as you learn or revise from these books, the important areas are, at all times, being related to clinical issues. This is seriously useful. It will benefit you beyond your exams and, together with the book's many helpful hints, will help you practise modern medicine when the time comes.

I hope you enjoy using this book, in spite of all the pre-exam stress, as much as I have enjoyed collaborating on it with Jason O'Neale Roach, Sarah Benyon (author of the first edition) and the excellent team from Elsevier.

Marek Dominiczak
Faculty Advisor

In the six years since the first editions were published, there have been many changes in medicine, and in the way it is taught. These second editions have been largely rewritten to take these changes into account, and keep *Crash Course* up to date for the twenty-first century. New material has been added to include recent research and all pharmacological and disease management information has been updated in line with current best practice. We've listened to feedback from hundreds of students who have been using *Crash Course* and have improved the structure and layout of the books accordingly: pathology material has been closely integrated with the relevant basic medical science; there are more MCQs and the clarity of text and figures is better than ever.

The principles on which we developed the series remain the same, however. Medicine is a huge subject, and the last thing a student needs when exams are looming is to waste time assembling information from different sources, and wading through pages of irrelevant detail. As before, *Crash Course* brings you all the information you need, in compact, manageable volumes that integrate basic medical science with clinical practice. We still tread the fine line between producing clear, concise text and providing enough detail for those aiming at distinction. The series is still written by medical students with recent exam experience, and checked for accuracy by senior faculty members from across the UK.

I wish you the best of luck in your future careers!

Dr Dan Horton-Szar
Series Editor (Basic Medical Sciences)

Acknowledgements

I would like to thank Sarah Benyon for creating an incredible first edition.

Figure acknowledgements

Fig 1.2 redrawn with permission from R Bronk. Human Metabolism. Addison Wesley Longman, 1999

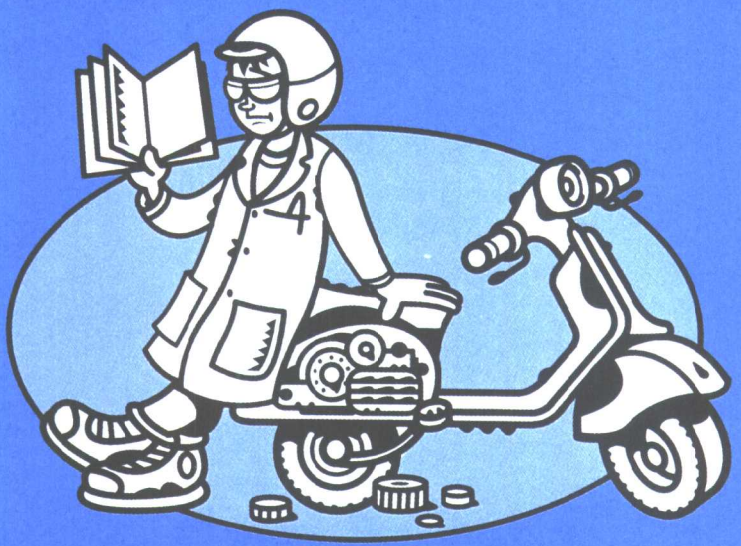
Fig 14.1 and 14.11 redrawn with permission from J W Marshall. Clinical Chemistry, 3rd edition. Mosby, 1995

Dedication

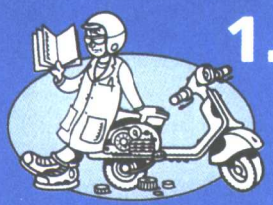
Soli Deo Gloria

To my teachers: Rob Williams,
Barbara Moreland,
Francis Reed and Phil Eaton,
for bringing molecular biology to life,
and to my parents for everything else.

Contents



METABOLIC PROCESSES AND NUTRITION



1. Overview of Metabolism

Useful definitions

Metabolism

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

- Each reaction does not occur in isolation but provides a substrate (the substance on which an enzyme acts) for the next.
- Pathways are built up in which the end product forms a substrate for other pathways, producing a continuous process.
- Many people compare metabolism to a 'map', in which the pathways are like roads with 'stop-off points' (intermediates) along the way.
- Roads need traffic lights and speed humps (regulatory mechanisms) to control the amount and speed of traffic.
- 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 that comes from the hydrolysis of ATP. Some examples of catabolic and anabolic pathways are shown in Fig. 1.1 and a scheme of overall metabolism is given in Fig. 1.2.

Metabolic pathways were not just invented to make the first year at medical school very dull! Do not get bogged down remembering every single step and enzyme in a pathway, as 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 the tissues in which they are particularly important.

The best way to revise metabolism is to draw simplified cycles of all the pathways, listing the six key criteria in Fig. 1.3 for each: purpose/function, location, site, reaction sequence, key steps and effect of inhibition.

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 speed of the entire 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'.

Metabolic pathways may occur in different cell compartments, different cells and in different tissues

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	glycogenesis: glycogen synthesis
proteolysis: protein breakdown	protein synthesis
lipolysis: fatty acid breakdown	lipogenesis: fatty acid synthesis
glycolysis: glucose breakdown	gluconeogenesis: glucose synthesis

Fig. 1.1 Examples of catabolic and anabolic pathways.

of the body at the same time. The pathways are carefully regulated, to ensure that the production of energy and intermediates meets the needs of the individual cell and 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 conditions, such as the fed state as opposed to starvation, or periods of exercise. These control mechanisms 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 effectors bind to regulatory sites on an enzyme that are distinct from the catalytic (active) site. They may increase or decrease an enzyme's activity. Often, allosteric control is exerted by the end-product of a pathway; this may be positive (stimulate pathway) or negative (inhibit pathway).

Hormonal control

There are two possible mechanisms by which 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 ensures that 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 enzyme induction. Hormones can 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 Gibbs 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) (°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.

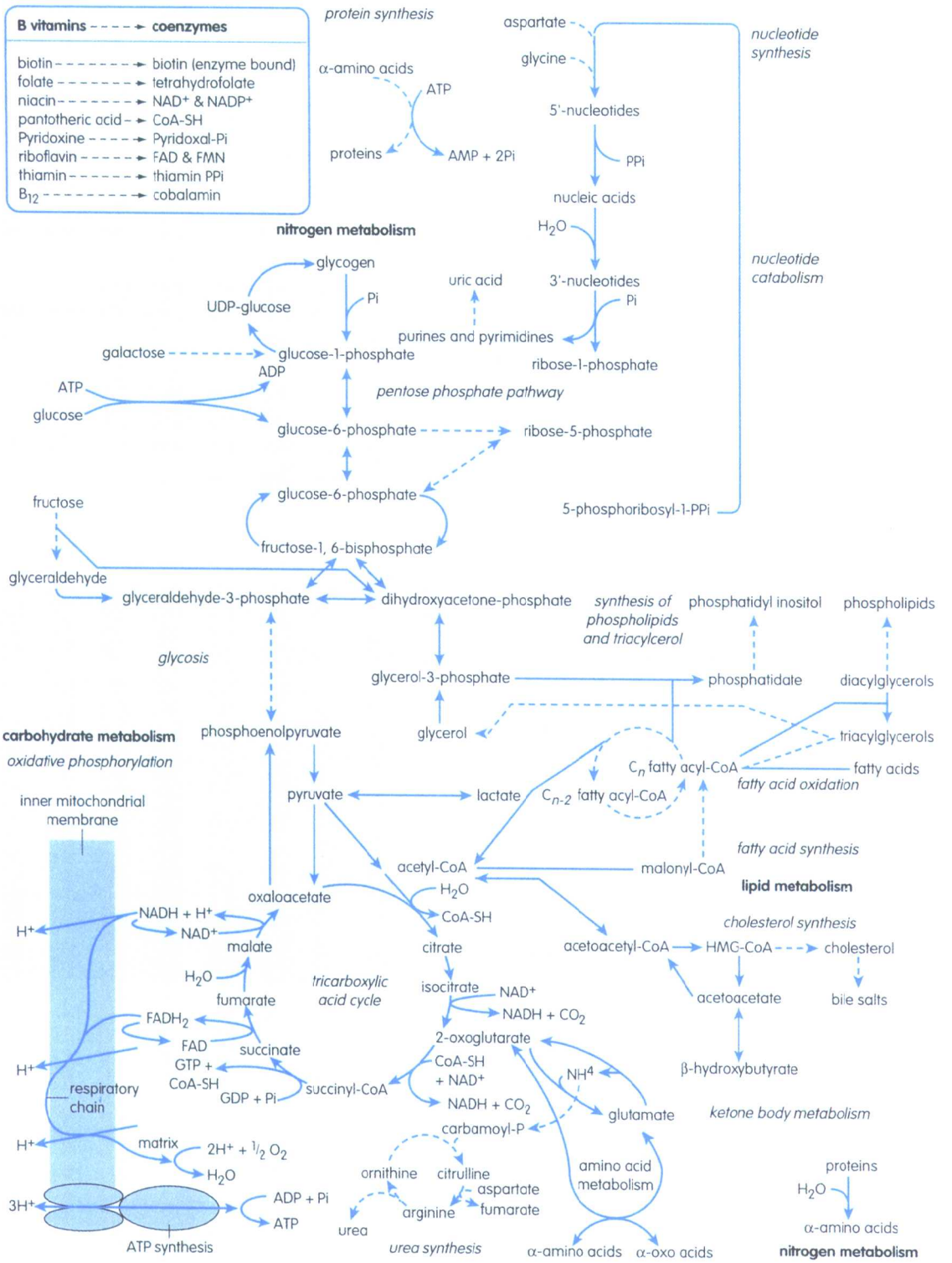


Fig. 1.2 A scheme of overall metabolism.

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
Tissue 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
Cell 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
Key steps: either those which form major control sites or those which are main 'branch points'	hexokinase reaction phosphofructokinase reaction 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. 1.3 Key points for remembering a metabolic pathway.

- 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.

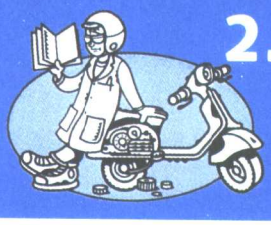
Be sure not to confuse exergonic and exothermic, and endergonic and endothermic. Exothermic reactions release heat during a reaction and have a negative enthalpy change ($-\Delta H$). Similarly, endothermic reactions absorb heat during a reaction and have a positive enthalpy change ($+\Delta H$). However,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

Free energy is required continuously for:

- Mechanical work, such as muscle contraction and cell movements.
- Active transport of molecules and ions.
- Synthesis of macromolecules and other molecules from simple precursors.

This energy is obtained in humans by the oxidation of foodstuffs. Some is transformed into a highly accessible form before use as the molecule adenosine triphosphate (see Chapter 2).

- 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 in metabolic pathways?
- What are the principles behind predicting the direction of a reaction?



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 (six carbons) to two three-carbon molecules of pyruvate. This sequence involves a net generation of two molecules of ATP and NADH (the reduced form of nicotinamide adenine dinucleotide). 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. Here it is oxidized by the tricarboxylic acid (TCA) cycle and oxidative phosphorylation to CO_2 and H_2O. This produces 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 a relatively 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 (RBCs), because they lack mitochondria and therefore glycolysis is their only energy-producing pathway.
- Exercising skeletal muscle, when oxidative metabolism cannot keep up with increased energy demand.
- The brain, because glucose is its main fuel (it uses about 120g/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.

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 be 'trapped' 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-

Examples of glucose transporters

Transporter	Location	Function
GLUT-1	erythrocytes and most cell membranes	Provides basal glucose transport to cells at a relatively constant rate
GLUT-2	liver and 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. Insulin promotes glucose uptake by muscle and fat. 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

Fig. 2.1 Examples of glucose transporters.

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'.

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).

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:

$$\text{Glucose} + 2\text{NAD}^+ + 2\text{ADP} + 2\text{Pi} \rightarrow 2\text{NADH} + 2\text{pyruvate} + 2\text{ATP} + 2\text{H}_2\text{O} + 2\text{H}^+$$

The name of an enzyme can be easily worked out, if you forget it, by knowing the name of the substrate (or the product) and the type of reaction involved (Fig. 2.4). For example, pyruvate is phosphorylated by pyruvate kinase.

Synthesis of ATP

ATP can be synthesized from ADP by two processes: substrate-level phosphorylation and oxidative phosphorylation.

Substrate-level phosphorylation

Substrate-level phosphorylation is the formation of ATP by the direct phosphorylation of ADP, that is, the direct transfer of a phosphoryl group from a 'high-energy' intermediate to ADP. It does not require oxygen and is therefore important for ATP generation in tissues short of oxygen, for example in exercising skeletal muscle. Reactions 7 and 10 of glycolysis (see Fig. 2.2) are both examples of substrate-level phosphorylation. Further examples are found in Fig. 2.25.

Oxidative phosphorylation

Oxidative phosphorylation requires oxygen and is the most important mechanism for the synthesis of ATP. It involves the oxidation of two nucleotides: NADH and the reduced form of flavin adenine dinucleotide ($FADH_2$) by the electron transport chain. This is discussed fully on p. 26.

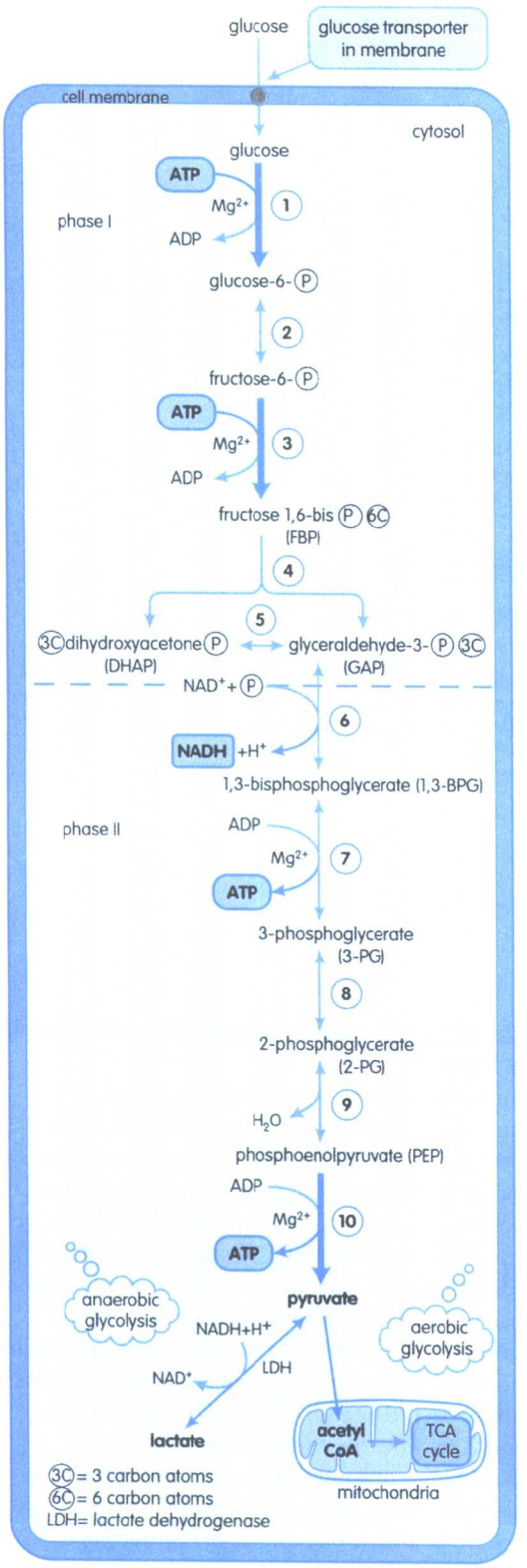
Energy yield of glycolysis

Anaerobic glycolysis

The overall reaction can be written as:

$$\text{Glucose} + 2\text{Pi} + 2\text{ADP} \rightarrow 2\text{lactate} + 2\text{ATP} + 2\text{H}_2\text{O}$$

The net effect is the generation of two moles of ATP from the anaerobic oxidation of one mole of glucose (Fig. 2.5). There is no net production of NADH because it is used by lactate dehydrogenase to reduce pyruvate to lactate. It is important to remember that although anaerobic glycolysis only produces a small



amount of ATP, it is an extremely valuable energy source for cells when the oxygen supply is limited.

Aerobic glycolysis

The overall reaction can be written as:

$$\text{Glucose} + 2\text{Pi} + 2\text{NAD}^+ + 2\text{ADP} \rightarrow 2\text{pyruvate} + 2\text{ATP} + 2\text{NADH} + 2\text{H}^+ + \text{H}_2\text{O}$$

Two moles of NADH are generated from the oxidation of one mole of glucose; each NADH is oxidized by the electron transport chain to yield about 2.5 ATP. Therefore the net effect of aerobic glycolysis is the generation of 7 ATP per mole of glucose (2 directly by substrate-level phosphorylation and about 5 indirectly by oxidative phosphorylation) (see Fig. 2.5).

Importance of NAD^+ regeneration from NADH

NAD^+ is the primary oxidizing agent of glycolysis and an important cofactor for glyceraldehyde-3-phosphate dehydrogenase (reaction 6 in Fig. 2.2). However, there is only a limited amount of NAD^+ available. Therefore a major problem is its regeneration from NADH, which is essential for glycolysis to continue. There are three possible mechanisms for the regeneration of NAD^+:

- Firstly, under anaerobic conditions, pyruvate is reduced to lactate by lactate dehydrogenase, with the simultaneous oxidation of NADH to NAD^+ in the cell cytosol (see Fig. 2.2). This is a reversible reaction in which the direction is determined by the ratio of NADH to NAD^+.
- Secondly, under aerobic conditions, NADH is oxidized to NAD^+ by the electron transport chain in mitochondria. NADH must first enter the mitochondria, either via the glycerol-3-phosphate shuttle or the malate–aspartate shuttle (Figs 2.6 and 2.7).
- Thirdly, under anaerobic conditions in yeast (alcoholic fermentation), pyruvate is decarboxylated to CO_2 and acetaldehyde, which is then reduced by NADH to yield NAD^+ and ethanol.

Fig. 2.2 The glycolytic (Embden–Meyerhof) pathway. Glycolysis takes place in the cell cytosol and consists of two distinct phases—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.