INTRODUCTION

Metabolism is defined as the chemical processes by which cells produce the substances and energy needed to sustain life. It is subdivided into:

Anabolism - the phase of metabolism in which complex molecules, such as the proteins and fats that make up body tissue, are formed from simpler ones.

Catabolism - the metabolic breakdown of complex molecules into simpler ones, often resulting in release of energy.

The process of metabolism within the body changes as a result of surgery or acute illness and so is an important area of knowledge for anaesthetists and intensivists.

A key metabolic process within the body is the liberation of energy by breakdown of substances ingested as food. The major constituents of a normal diet are **carbohydrates, protein and fat.**

OVERVIEW OF METABOLISM

Figure 1 is an overview of the pathways by which the three major energy sources (fat, carbohydrate and protein) can be used to produce ATP, the main unit of energy within the body. Glucose is predominantly metabolized via glycolysis, free fatty acids via β-oxidation and proteins via deamination. The common endpoint for all three pathways is acetyl coenzyme A (acetyl coA), which can be used as a substrate for very efficient production of ATP via the citric acid cycle (also known as the Krebs or tricarboxylic acid cycle), when oxygen is available (aerobic metabolism). Acetyl coA is also the start point by which glycolysis can be reversed (gluconeogensis) - glucose is regenerated and used by specific glucose-requiring organs (the brain and heart) during fasting. All of these processes are explained in more detail below. It is important to understand the concept that different metabolic processes are going on in different organs at different times, dependent on the activities and requirements for energy of those tissues, and those of the body as a whole. For example, the liver may be breaking down glycogen to release glucose for the brain (glycogenolysis), whilst the fat is being broken down by β-oxidation for production of ATP via the Krebs cycle and production of glucose via gluconeogenesis. ATP cannot be transferred around the body, only produced and used within cells, so the body is dependant on efficient transfer of the metabolites and substrates shown in Figure 1 around the body, in order to meet the needs of individual organs under different conditions.

The body has various mechanisms that it can use to adjust to the availability of various substrates:

- They can be transformed into other types of substrate, or
- They can be transported around the body and used as needed by other organs to make ATP, which can then be used within the cells of that organ.
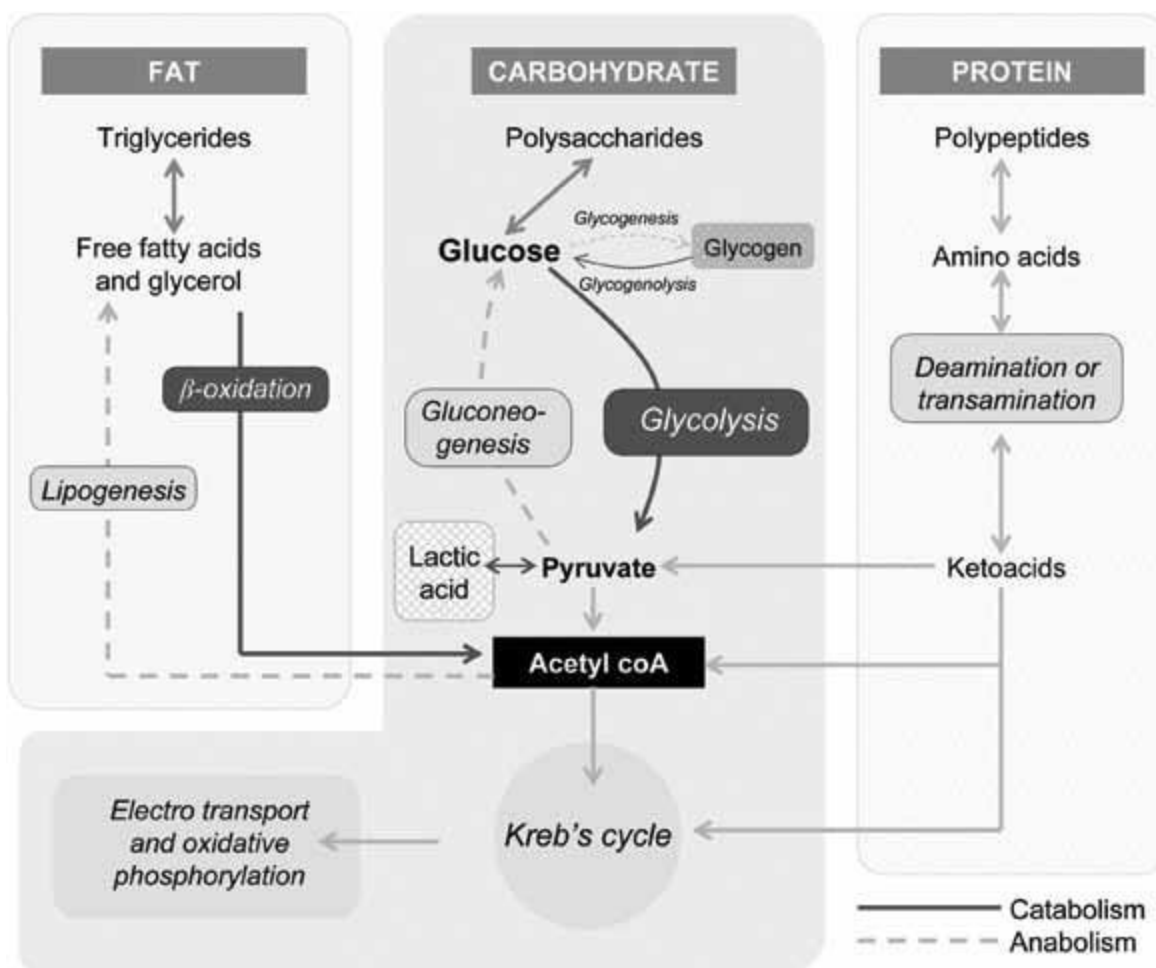
Figure 1. A highly simplified overview of fat, carbohydrate and protein metabolism

TYPES OF MOLECULES

Carbohydrates

Carbohydrate molecules contain carbon, hydrogen and oxygen atoms, usually in the proportion 1:2:1, and must contain both aldehyde and ketone groups.
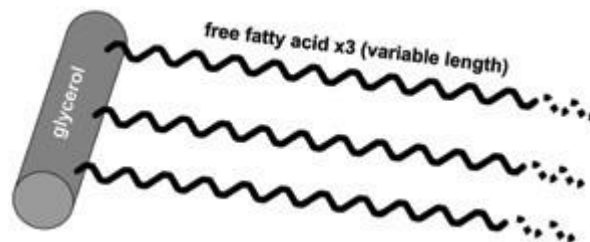

Figure 2. A- an aldehyde, B- a ketone

Carbohydrates in their most basic form are called monosaccharides, such as glucose. *Monosaccharide* units may be joined into chains to become polysaccharides, such as starch.

Fats

Fats are ingested as triglycerides and cholesterol. Triglycerides are esters of three fatty acids chains bonded to a glycerol molecule.
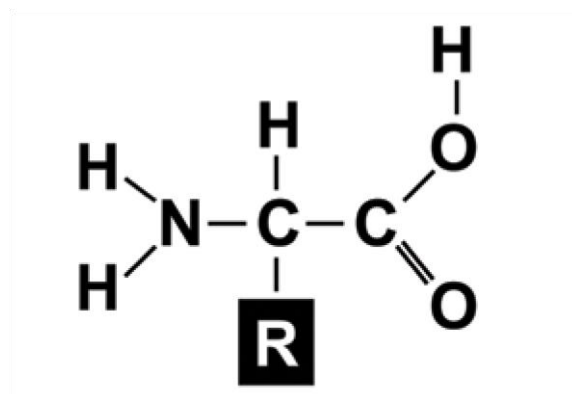

Figure 3. A triglyceride

Proteins

Proteins are chains of amino acids, molecules containing an amine group (nitrogen-containing, $-NH_2$), a carboxylic acid group (-COOH) and a specific side chain (R in Figure 4).

Figure 4. An amino acid

Energy

Energy is required for the body to perform activities or 'work'. This work can be external (skeletal muscle) or internal (cardiac muscle, biochemical processes). Under normal conditions it is obtained by breakdown of dietary carbohydrate, protein and fat. The average energy requirement for a 70kg man is 2500kcal per day. The basic unit for supply of energy for processes within the body is adenosine triphosphate (ATP), a molecule that has high energy bonds with its attached phosphate groups. The breakdown of adenosine triphosphate to adenosine diphosphate (ADP) releases energy. ATP can then be regenerated from ADP using either:

- energy generated within the cytoplasm by anaerobic respiration (no oxygen is required),

- aerobic respiration in mitochondria (oxygen requiring and far more productive of ATP), or

- by direct interaction with creatine phosphate.

Remember that ATP and ADP are intracellular molecules that provide energy *in situ* within a cell, but cannot be transferred around the body from one organ to another. Movement of energy sources around the body is achieved by the pathways for breakdown (catabolism) and build up (anabolism) of the substances shown in Figure 1.

Acetyl coenzyme A

Acetyl coA is the central converting substance that links together the metabolism of fat, carbohydrate and protein and so is known as the universal intermediate.

CARBOHYDRATE METABOLISM

The major process of ATP production is carbohydrate metabolism within cells. This is done via two main pathways: glycolysis and the citric acid cycle (Kreb's or tricarboxylic acid cycle). Glycolysis is the breakdown of glucose to form pyruvate. At some stages ATP is generated directly, at other stages a proton (H^+ ion) is passed to the coenzymes:

- NAD^+ (nicotine adenine dinucleotide) to become NADH and

- FAD (flavine adenine dinucleotide) to become $FADH_2$.

The protons are then passed on to a flavoprotein-cytochrome carrier chain within the cell's mitochondria to enable the process by which ATP is regenerated. They provide energy for this process by giving up an electron that is passed down the chain by sequential oxidation and reduction.

Glycolysis

Glucose, a six-carbon molecule ($C_6H_{12}O_6$), is cleaved to eventually form 2 pyruvate molecules each containing 3 carbon atoms (see Figure 1). Initially, glucose is transported into the cell and converted into glucose-6-phosphate (G-6-P) by an enzyme called hexokinase (or glucokinase). G-6-P is unable to move back across the cell membrane and therefore remains within the cell. The enzyme phosphohexose isomerase catalyses the reaction to form fructose-6-phosphate, which is then converted to fructose-1,6-biphosphate. This molecule is then split to form two 3-carbon molecules which then release their phosphate atoms over the next 2 steps of the reaction, releasing enough energy to generate ATP from ADP and phosphate. For each glucose molecule utilized in glycolysis, 4 ATP molecules are produced, however, the process requires 2 ATP molecules, resulting in a net production of 2 ATP molecules per glucose molecule.
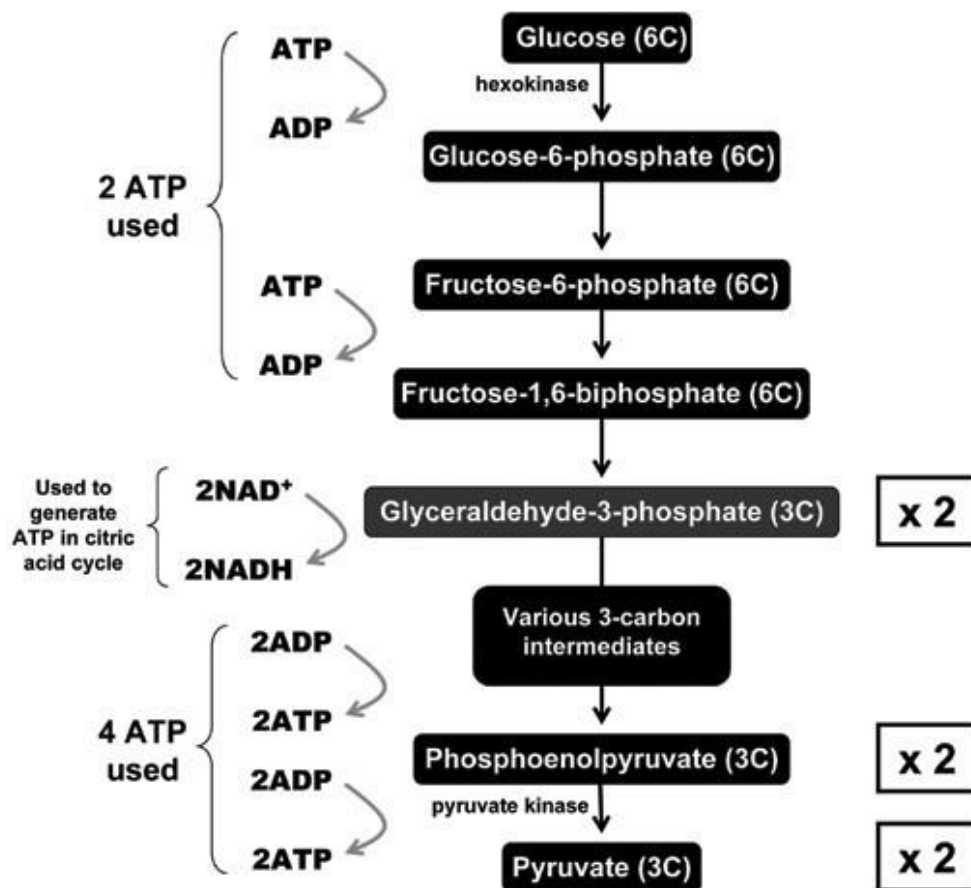

Figure 5. Simplified overview of glycolysis

Under aerobic conditions (oxygen is available) pyruvate then enters the mitochondria and is broken down into acetyl coenzyme A which is the main substrate of the citric acid cycle. The citric acid cycle is a progressive breakdown of citrate, a 6-carbon molecule, into oxaloacetate, a 4-carbon molecule.
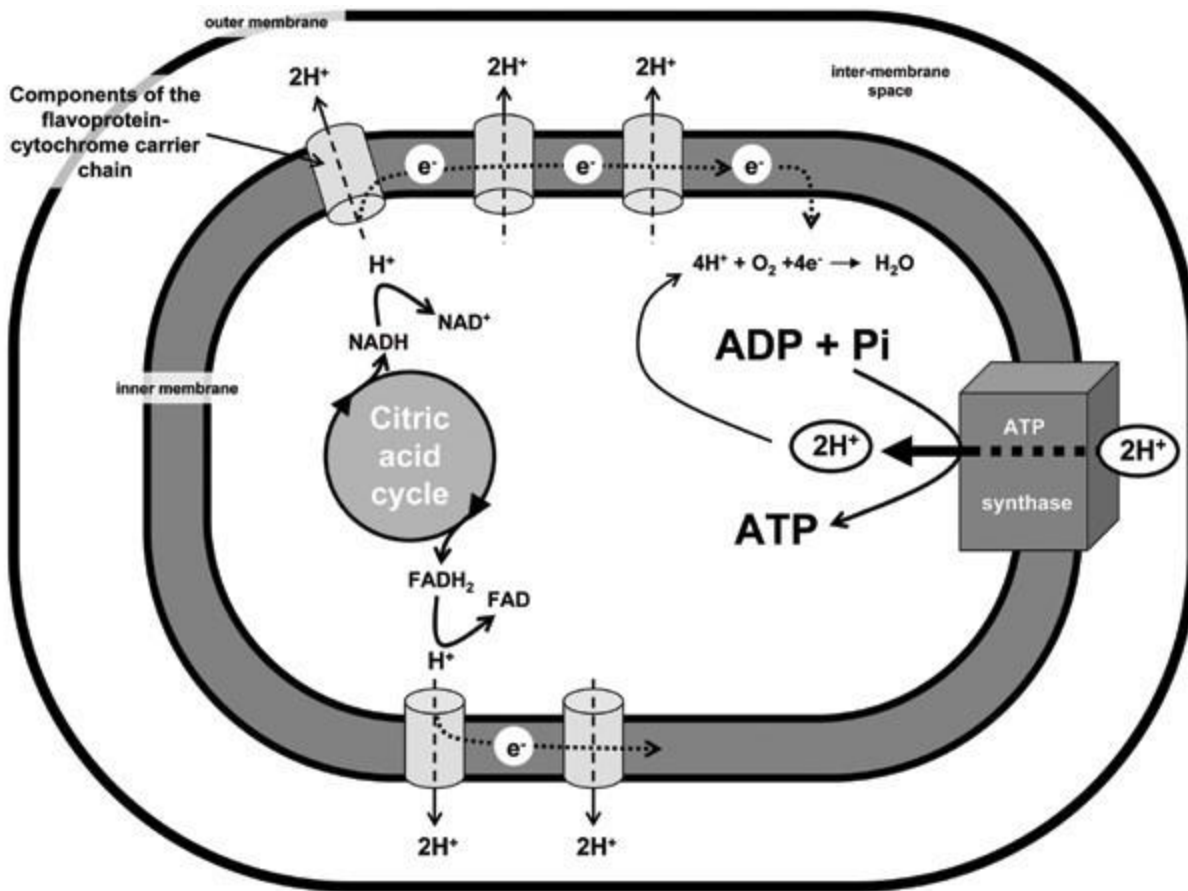
The citric acid cycle

The acetyl coenzyme A produced by glycolysis combines with oxaloacetate to reproduce citrate. This metabolic process is dependant on a supply of acetyl coenzyme A and production of oxaloacetate, as well as the presence of oxygen, without which pyruvate will not cross into the mitochondria.
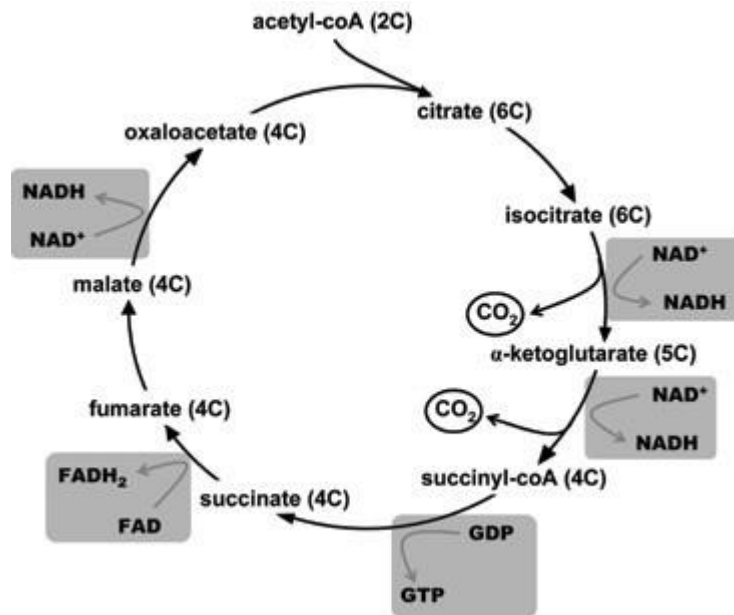
Figure 6. The citric acid cycle (also known as the tricarboxylic acid cycle and the Kreb's cycle)

For each acetyl coenzyme A molecule that enters the citric acid cycle, 6 nicotinamide adenine dinucleotide molecules and 2 flavin adenine dinucleotide molecules gain a proton to become NADH and $FADH_2$.

These compounds liberate electrons to a series of flavoproteincytochrome carriers mounted on the inner mitochondrial membrane (see Figure 7). The electron is passed from carrier to carrier in a series of oxidation/reduction reactions, liberating energy that is used to pump the protons (H^+) from NADH and FADH across the inner membrane to the inter-membrane space This creates an H^+ concentration gradient across the inner membrane, generating H^+ flow across channels containing ATP synthase. H^+ flow through the synthase complex provides energy for formation of ATP. Oxygen acts as the final electron acceptor at the end of the electron transport chain ($O_2 + 4e^- + 4H^+ = 2H_2O$). Without oxygen, the electron transport chain cannot function.

outer membrane

Components of the
flavoprotein-
cytochrome carrier
chain

inter-membrane
space

2H+   2H+   2H+

e⁻   e⁻   e⁻   e⁻

H⁺

$4H^+ + O_2 + 4e^- \rightarrow H_2O$

NADH   NAD⁺

inner membrane

ADP + Pi

Citric
acid
cycle

2H⁺   ←   ATP
synthase   2H⁺

ATP

$FADH_2$ FAD

H⁺

e⁻

2H⁺   2H⁺

ATP

Figure 7. Schematic drawing of generation of ATP
using energy derived from NADH and FADH₂

The production of ATP at each stage can be seen in Table 1. The net result is that for each glucose molecule, metabolised under aerobic conditions, 38 ATP molecules are produced. Acetyl coenzyme A can also be produced by breakdown of fat and protein. Fatty acids are transported into mitochondria where they undergo β-oxidation, combining with coenzyme A to form acetyl coenzyme A. Amino acids undergo oxidative deamination or transamination (the amine group is converted into urea) to form keto acids, which can then be broken down to form acetyl coenzyme A.

Under anaerobic conditions pyruvate is not converted to acetyl coenzyme A, but instead to lactate which is transported out of the cell. The total ATP yield from each glucose molecule under anaerobic conditions is 2 ATP molecules, making it much less efficient than aerobic metabolism.

Carbohydrate that is not immediately needed after absorption into the body, is stored as glycogen in the liver and skeletal muscle. An average 70kg man stores up to 500g of glycogen at any one time. It is formed by glycogenesis in which glucose molecules are sequentially added to existing glycogen chains. The process is activated by insulin which is secreted from the pancreas in response to high glucose levels.

The major enzyme responsible for glycogenesis is glycogen synthase.

Stage		Net number of ATP produced
Glycolysis	**2ATP** (4 produced – 2 consumed)	**2**
Conversion of pyruvate to acetyl coA	2[3(3 NADH + 2H$^+$)] = **2 x 6ATP**	**12**
Citric acid cycle	**2 x 1 ATP** 2 X 3[3(NADH + H$^+$)] = **2 X 9ATP** 2 X 2(FADH$_2$) = **2 X 2ATP**	**24**
Total ATP	**2 + 12 + 24**	**38**

Table 1. Summary of ATP molecules produced at each stage of glucose metabolism

FAT METABOLISM

Fat is an energy dense substrate capable of yielding 9kcal.g^{-1} (in comparison to 4kcal.g^{-1} from carbohydrate). It is stored as triglyceride in adipose tissue, each triglyceride being composed of three fatty acid chains and a glycerol molecule (Figure 3). In times of adequate nutrition, circulating insulin stimulates lipogenesis. When carbohydrate intake or stores (glycogen) are insufficient for the energy requirements of the body, glucagon causes triglycerides to be broken down into fatty acids and glycerol by the action of the enzyme lipase. Fatty acids are cleaved into 2-carbon molecules (β-oxidation) which are then converted into acetyl coenzyme A which can either feed into the citric acid cycle or be a substrate for gluconeogenesis to generate glucose. Glycerol can also be used in gluconeogenesis.

PROTEIN METABOLISM

Proteins are large molecules consisting of varying combinations of amino acids linked together. They have numerous important roles in the structure and function of the body such as in muscle, haemoglobin, hormones, fibrin and receptors. They are only used as a source of energy in extreme circumstances. Amino acids consist of carbon, hydrogen, oxygen and an amine group (Figure 4), with some containing sulphur, phosphorous or iron atoms. Branched chain amino acids (such as valine, leucine and isoleucine) are commonly used for energy production. The amino acids undergo oxidative deamination or transamination (the amine group removed from the molecule and converted into urea) to form ketoacids, which can then be broken down to form acetyl coenzyme A. This can be used in the citric acid cycle to produce ATP.

In normal subjects the metabolism of protein is inhibited by the presence of circulating glucose. Only a small glucose intake is required to increase the circulating concentration of insulin to levels which block protein breakdown. Use of high energy glucose drinks on the morning of surgery as part of enhanced recovery programs aims to avoid or delay the catabolic response to surgery.

STARVATION

Starvation is defined as an absence or inadequacy of exogenous intake and may be partial or complete. The body must survive totally or in part on its internal stores. Starvation initially results in a fall in plasma glucose which triggers a decrease in insulin and an increase in glucagon secretion. This halts glycogenesis and starts the process of glycogenolysis. Glycogen is broken down to glucose-6phosphate and then to glucose which is distributed to the organs that exclusively metabolise glucose (the brain and heart). Glycogen stores last 24 hours, after which other sources of energy must be utilized.

Gluconeogenesis is the process by which glucose is formed form a number of alternative endogenous sources - it is effectively glycolysis in reverse, and so requires energy to proceed. Glucose production is essential as the brain cannot utilize energy substrates such as lactate and pyruvate. Potential substrates for gluconeogenesis are pyruvate, lactate, amino acids and glycerol. Fatty acids and ketones cannot be used for gluconeogenesis. The process is stimulated by a decrease in circulating insulin concentration and increased glucagon.

Amino acid use for gluconeogenesis is inefficient with 1.75g of protein being required to produce 1g of glucose. Glycerol, produced by breakdown of triglycerides, and lactate are alternatives. They are transported to the liver to provide substrates for gluconeogensis.

After 48 hours of starvation, or extreme exercise such as running a marathon, ketogenesis becomes a major source of energy. It has been referred to as the 'final adaptive process in starvation'. Free fatty acids are metabolized to form ketone bodies, namely acetoacetate and β-hydroxybutarate. These can be used by all tissue (including the brain) as an alternative energy source to glucose. Ketogenesis occurs in response to low insulin and high glucagons levels. It can be profound in diabetic ketoacidosis when no insulin is present, allowing glucagon to exert its influence unopposed.

The metabolic processes described in this article are essential for life and are subject to massive variation depending on the individual's environment, nutritional state and level of exercise or stress. The clinical relevance becomes clear when considering performing major surgery on a fasted patient. Maintaining an adequate nutritional intake preoperatively and oxygen delivery intraoperatively are vitally important in avoiding detrimental catabolic and anaerobic metabolic processes in patients undergoing major surgery and those with critical illness.