13 Metabolism

Summary

The cell turns fuel into a form of energy that can be used by the body. Human body cells must also act together to maintain the internal environment of the body constant insofar as temperature, pH and osmolality are concerned. Energy production by the cell usually proceeds with an oxygen supply (aerobic metabolism) delivered in the blood in association with haemoglobin. A limited amount of energy can be produced without oxygen (anaerobic metabolism). The energy store of the cell is adenosine triphosphate (ATP). Cells are also involved in making compounds that are not fuels, such as nucleic acids and haemoglobin. Waste products such as carbon dioxide, water, ammonia, urea, and uric acid are also generated. Sometimes metabolic pathways are deficient in the cell and the compounds they would ordinarily use reach toxic levels. These compounds must then be avoided in the diet.

High energy bonds

Adenosine triphosphate (ATP) (figure 13.1) is the energy storehouse of the body, and it is found in every cell. It is the final common pathway for the provision of energy for most body functions (see chapter 14, Energy). Where the chemical bond formed between phosphoric acid and organic compounds* is of the high energy type, it can yield on hydrolysis 10–12 kcal/mol (42–50 kJ/mol); by contrast the low energy type bond yields 2–3 kcal/mol (8–13 kJ/mol).

The functions of ATP are

1. to provide energy for
(a) active transport of compounds across cell membranes*,
(b) formation of chemical compounds, and
(c) muscular contraction* (figure 13.2).
2. to act as the precursor for 'cyclic-AMP' (cyclic adenosine 3',5' monophosphate), which acts as an intracellular ('second') messenger for signals which reach the cell membrane ('first messengers'). Hormones* are examples of first messengers.

Organic compounds or molecules: hydrocarbons (containing hydrogen and carbon atoms) and their derivatives (often containing oxygen and sometimes containing nitrogen or sulphur atoms).

Cell membrane: surrounds the cell and is made up of protein, phospholipid and cholesterol (see chapter 17, Lipids). It allows some substances to pass through and excludes others.

Muscular contraction: the contraction of muscle, whether skeletal, smooth (as in the gut, blood vessels or uterus) or cardiac, is dependent on small fibres within the cell. The fibre proteins, actin and myosin, slide over one another when energy from ATP is released.

Hormones: compounds produced in one site (for example the pituitary gland, thyroid gland, adrenal gland, parathyroid glands, ovaries or testes, pancreatic islets, the gut) and transported in the blood to act at a distant site.

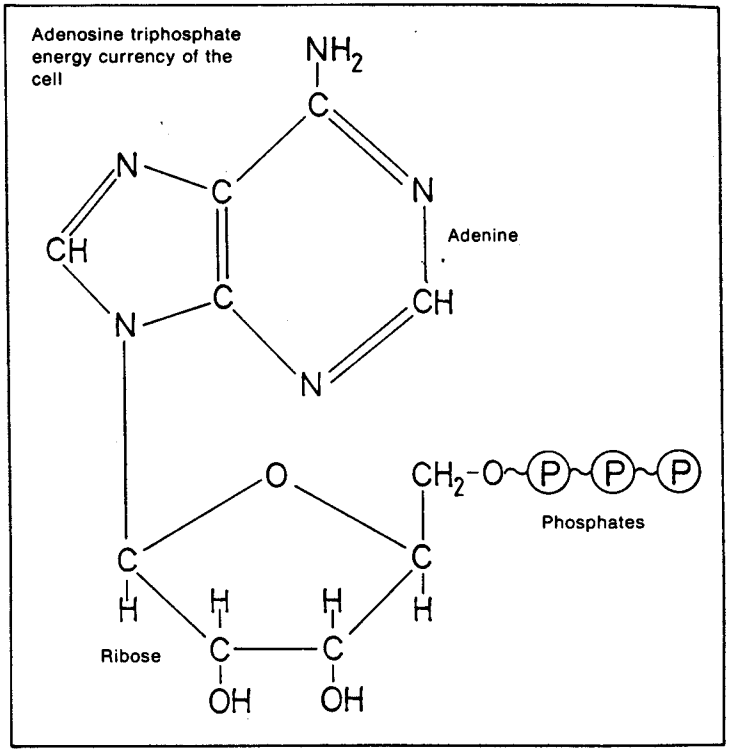


Figure 13.1 Adenosine triphosphate, the energy storehouse of the body and provider of cyclic AMP, an important cell messenger. It can be produced in the cytoplasm of the cell without oxygen or in the cell mitochondrion with oxygen.

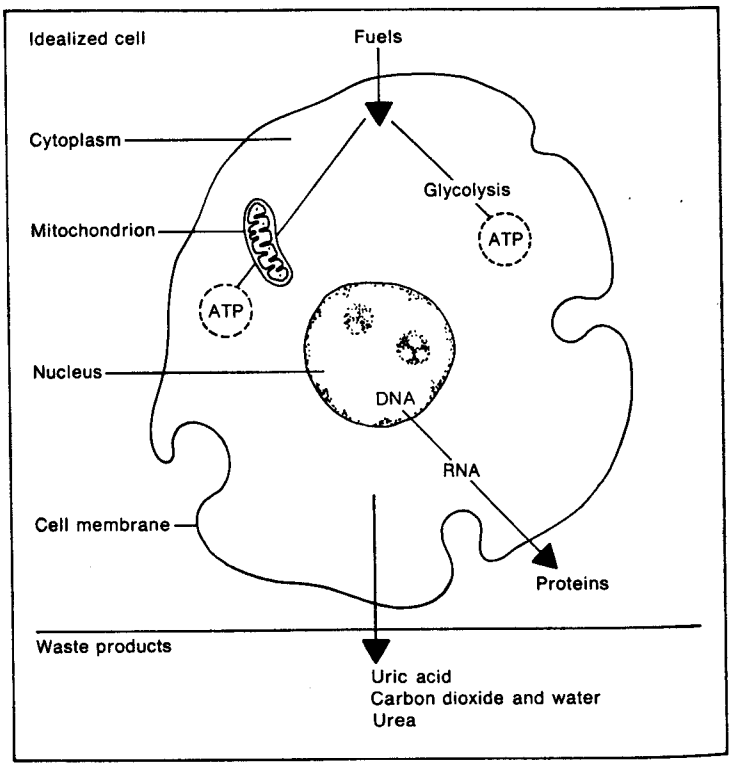


Figure 13.2 An example of a body cell and its components. In the case of a muscle cell, the work of contraction is done by subcellular structures known as myofibrils.

The following are compounds with high energy bonds:

1. ATP (adenosine triphosphate)
2. ADP (adenosine diphosphate)
3. Creatine phosphate (phosphocreatine)
4. Thioesters such as Coenzyme A (CoA)
5. Other nucleotide triphosphates.

Creatine phosphate can serve to maintain the supply of ATP, which is required for muscle contractions. Acetyl CoA is an example of a CoA derivative which, because of the extra energy, allows acetate to enter reactions which it otherwise could not.

ATP is formed from ADP when hydrogen is transferred from NADH* to flavoproteins (see chapter 20, Vitamins). This hydrogen is transferred along what is called the respiratory chain of flavoproteins and cytochromes* until finally accepted by oxygen, so forming water. Ultimately oxygen is necessary, therefore, for ATP to be formed. The formation of NADH requires the availability of NAD and the removal of hydrogen (one form of biologic oxidation) from an organic compound.

If oxygen is not available NADH can give its hydrogen to pyruvic acid, so forming lactic acid. Since NADH can be generated during the conversion of glucose to pyruvate, the overall conversion of glucose to lactic acid is an anaerobic (no oxygen required) way of producing ATP.

When oxygen is available, pyruvic acid can be converted to acetyl CoA with the aid of the enzyme pyruvate dehydrogenase (PDH). Acetyl CoA is then converted to citric acid, which enters the citric acid cycle (Krebs cycle). With the progressive removal of hydrogens (which end up combining with oxygen to form water) carbon dioxide (CO_2) is formed from substrates. But it should be noted that only glucose and not fatty acid (such as palmitic acid) or pyruvic acid, or lactic acid could provide ATP anaerobically.

Whereas anaerobic metabolism takes place in the cytoplasm of the cell, aerobic metabolism takes place in the mitochondrion, a subcellular organelle.

NADH: nicotinamide adenine dinucleotide (NAD) and dihydronicotinamide adenine dinucleotide (NADH) constitute a hydrogen pick-up system for transfer of hydrogen to the flavoprotein–cytochrome system. Nicotinic acid forms part of the molecule.

The flavoprotein–cytochrome system is a chain of enzymes in the mitochondria that transfers hydrogen to oxygen. Flavoprotein contains a derivative of the vitamin riboflavin and cytochrome contains iron rather like haemoglobin.

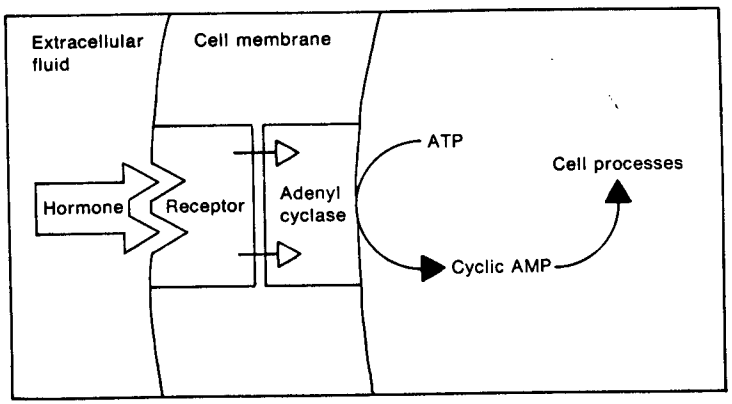


Figure 13.3a ATP as a source of the cell messenger, cyclic AMP

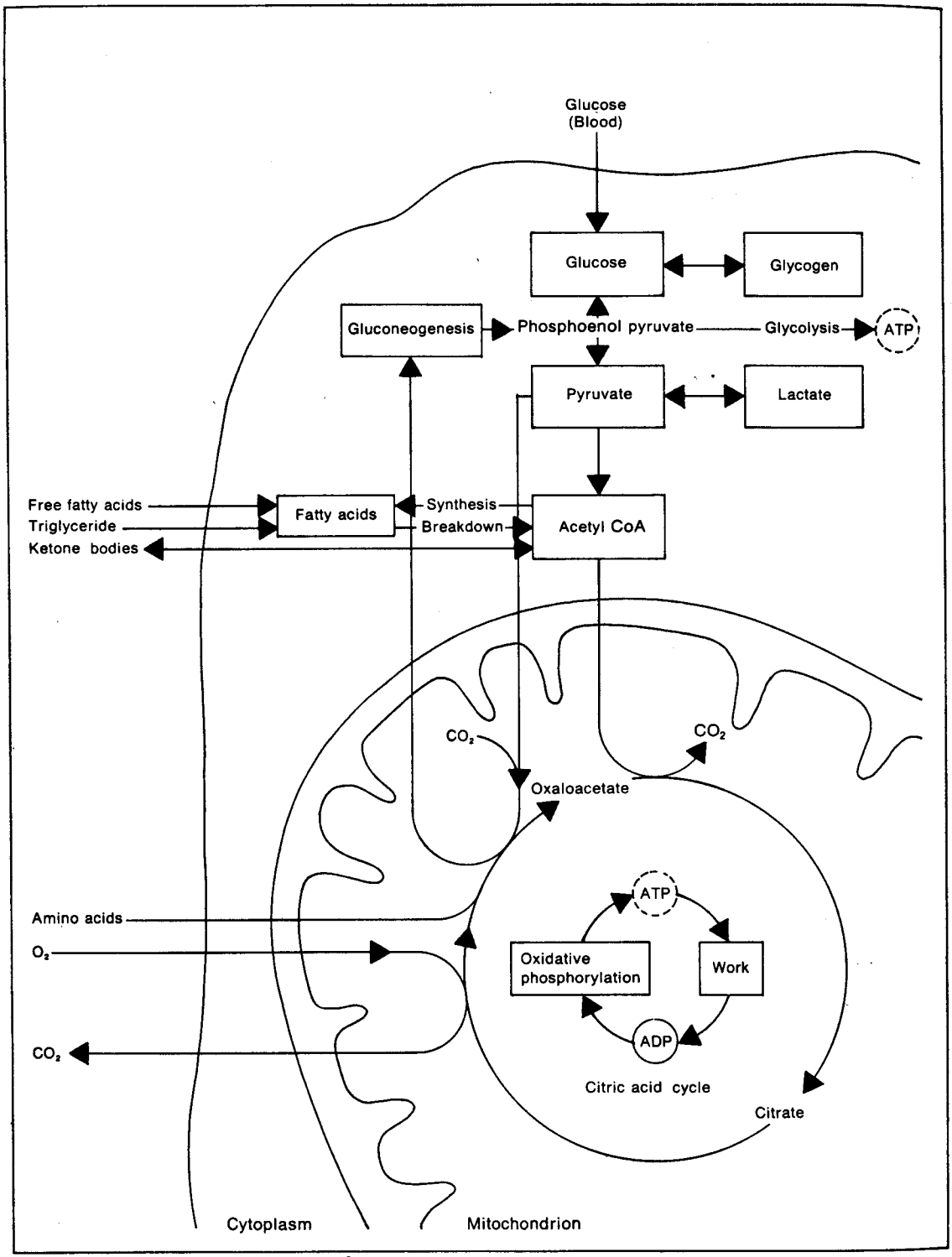


Figure 13.3b Metabolic pathways for energy production in the cell

Energy stores

Apart from the storage of energy as high energy bonds, substrates or fuels for manufacture of those bonds can also be stored in cells. These can be in the following two forms:

1. glycogen: a polymer of the carbohydrate glucose found in animal cells (chapter 10, Food preparation; chapter 15, Carbohydrates), and
2. triglyceride: a lipid or fat store consisting of three fatty acid molecules linked to a glycerol molecule (see chapter 17, Lipids).

The nutritional state, especially the energy balance, of the individual can influence glycogen and triglyceride stores. The formation and breakdown of these energy stores is under the influence of hormones (such as insulin, adrenaline, cortisol, glucagon) and the nervous system (the 'autonomic nervous system', the system which operates subconsciously). Both stores can be called on during starvation and during exercise (see chapter 14, Energy).

In a reference man of 70 kg, the energy stores are:

1. carbohydrate 8000kJ (1900 kcal)
(a) Muscle glycogen 350 g
(b) Liver glycogen 85 g
(c) Extracellular glucose 20 g
2. fat 588 000 kJ (140 000 kcal).

Fuels in the blood

In steady state conditions, there will be no net change in the intracellular energy stores of glycogen and triglyceride. However, the tissue fuel-needs will be met by the blood supplies. In the fasting state, the major fuel is free fatty acid for skeletal and cardiac muscle, with lesser contributions from glucose and triglyceride and even smaller contributions from lactate, pyruvate, acetate and ketone bodies. However, the brain depends almost exclusively on blood glucose during an overnight fast. With prolonged starvation, the brain begins to utilize ketone bodies (acetone, acetoacetate, betahydroxybutyrate) instead of glucose. Depending on the kind of meal, in the fed state, glucose and chylomicron triglyceride (see chapter 17, Lipids) become more important sources of fuel for muscle.

Table 13.1 Fuels in blood

Carbohydrate	*Lipid*
Glucose	*Free fatty acids (FFA)*
Lactate	*Triglyceride*
Pyruvate	*(a) chylomicron*
	(b) very low density lipoprotein (VLDL)
	Acetate
	Ketone bodies

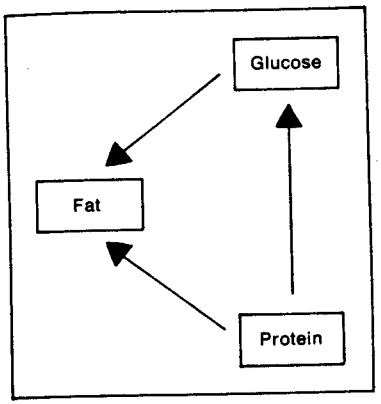


Figure 13.4 Substrate interconversions that are possible

The way in which the relative contribution of a fuel to oxidative metabolism is worked out is to calculate the oxygen extraction ratio (OER).

$$\text{OER} = \frac{\text{(arteriovenous difference in fuel concentration)} \times \text{(oxygen equivalent of substrate)}}{\text{arteriovenous difference in oxygen concentration}}$$

The OER is that proportion of oxygen consumed by a tissue which would be used by the fuel if it were completely oxidized. The oxygen equivalent can be worked out from the equation, which shows the number of molecules of oxygen required to completely oxidize a given number of molecules of substrate to carbon dioxide and water.

Whereas fat can be produced from both protein and glucose, glucose can only be produced from protein. (Full interconversions are shown in figure 13.4.) However, when the breakdown of fat occurs, free fatty acid flux from adipose tissue to the liver increases, and this stimulates hepatic gluconeogenesis* (figure 13.5).

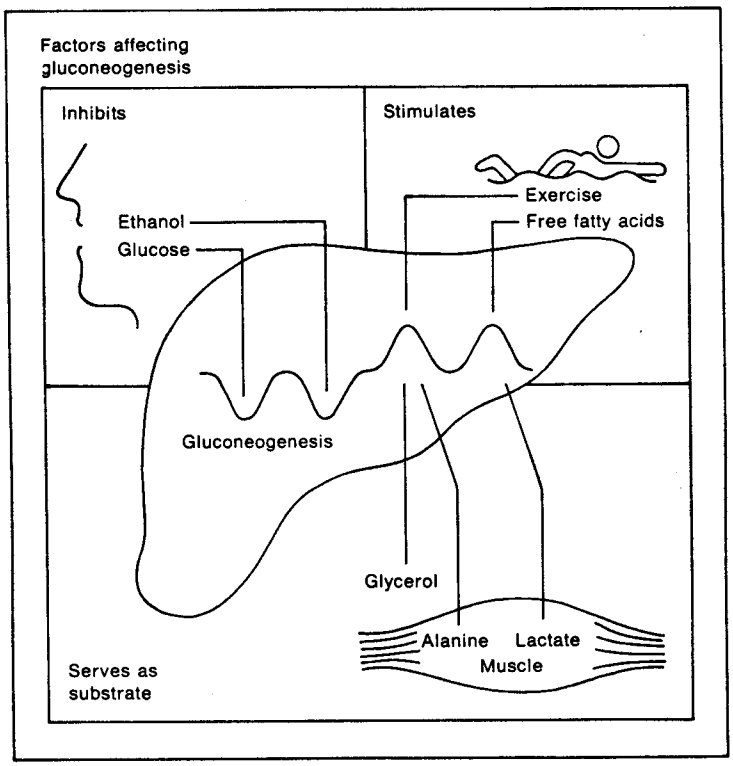
Hepatic gluconeogenesis: the new formation of glucose in the liver.

Compounds that are not fuels

Nucleic acids

The principal role of nucleic acids is to transmit information about

Figure 13.5 Factors affecting gluconeogenesis



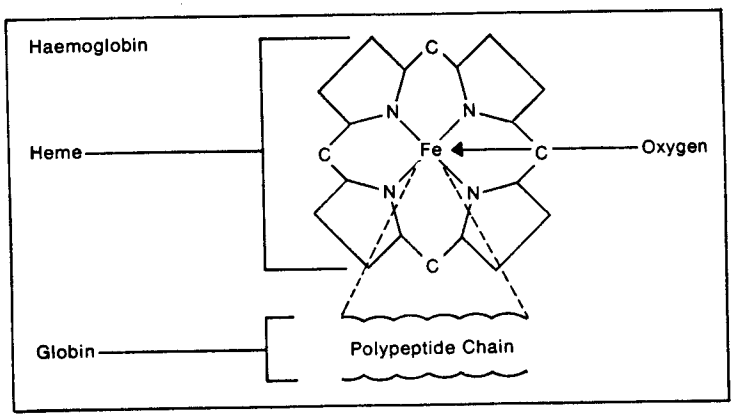


Figure 13.6 Haemoglobin molecule

the composition of proteins, either as part of DNA (deoxyribonucleic acid) or RNA (ribonucleic acid). DNA and RNA are nucleotide polymers.

Base		*Sugar*	
Purine or Pyrimidine	+	Ribose or Deoxyribose	= Nucleoside
Nucleoside	+	Phosphate	= Nucleotide

Purines (adenine, guanine, xanthine) and pyrimidines (cytosine, uracil, thymine) are important not only as component of nucleic acids and therefore DNA and RNA, but also of compounds with high energy bonds.

Nucleic acids in the diet are digested, and the purines and pyrimidines they contain are absorbed. However, most of the body's purines and pyrimidines are formed from amino acids, mainly in the liver.

Vitamins particularly important in the synthesis of nucleic acids are vitamin B_{12} (cobalamin) and folic acid (folacin). When these vitamins are lacking, cell division decreases and this is especially evident in the formation of blood cells (see chapter 20, Vitamins).

Haemoglobin

Haemoglobin is an oxygen-transport compound found in red blood cells (erythrocytes). Oxygen is collected on passage of the red blood cells through the lungs and delivered to the tissues where it is required for cellular respiration and energy formation (see ATP formation above).

Haemoglobin can be thought of as consisting of two parts, a protein globin and heme. The heme part consists of a porphyrin molecule with iron (Fe^{++}) in the middle. Oxygen attaches to the heme part of the molecule (figure 13.6). For the formation of the haemoglobin molecule, good protein and iron nutrition are required and deficiencies of both are, therefore, associated with anaemia (inadequate red cell mass).

Waste products

When carbohydrate, fat and protein are used as energy sources, the end products include carbon dioxide and water. This water contributes to water balance (see chapter 19, Water) as 'metabolic

water'. The carbon dioxide adds to the acid load of the body that must be buffered. This acid load is dealt with by the exhalation of carbon dioxide from the lungs or the excretion of acid in the urine.

The catabolism (breakdown) of protein or of pyrimidines ultimately yields ammonia. This can, in turn, be converted to urea in the urea cycle (Krebs-Henseleit cycle) (see chapter 18, Protein).

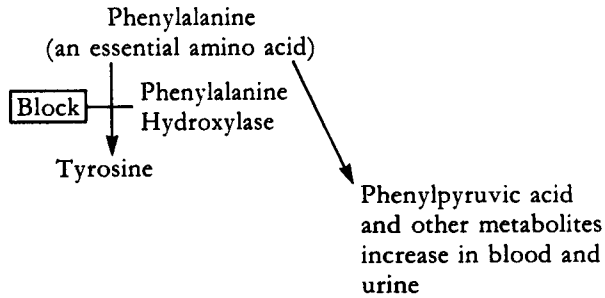
Purines (especially from the dietary items rich in nucleic acids such as organ meats and from purines synthesized by the body) are ultimately converted to uric acid which must be excreted in the urine. Other acids, such as lactic acid, formed with alcohol abuse can compete with uric acid for excretion by the kidney. Therefore, alcohol abuse can lead to high uric acid concentrations in blood and even to gout.

Errors of metabolism

When dietary components are absorbed, but not metabolized in the usual way, they or alternative products of metabolism can be toxic. To avoid these toxic effects, the component can often be excluded from the diet. One problem with such exclusions is that the particular component can be essential for man and a deficiency may be evident.

Phenylketonuria (PKU)

In this condition, the enzyme 'phenylalanine hydroxylase' is not made or made in insufficient quantities. Enzymes are proteins, so this defect represents an hereditary problem with that part of the DNA responsible for transmitting the information related to this protein's synthesis. It affects about 1 in 10000 infants who have inherited one recessive gene from each parent to give the two recessive genes required for expression.



It is thought that the accumulation of phenylpyruvic acid inhibits the formation of the neurotransmitter serotonin from tryptophane (see chapter 34, Nutrition and the brain). This problem in neurotransmission leads to mental deficiency. By the early recognition of phenylketunoria and the avoidance of phenylalanine from protein in the diet, intellectual handicap can be avoided.

Lactase deficiency

Although all human beings are born with intestinal lactase to allow the digestion of human breast milk lactose, beyond infancy about 85 per cent of the world's population is unable or poorly able to digest lactose. This enzyme deficiency can lead to diarrhoea when milk sugar is ingested. Lactose deficiency also occurs as a result of infective diarrhoea (see chapter 12, Digestion and absorption).

Further reading

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Questions

1. What is the difference between a nutrient that serves as a fuel and one that does not?
2. Describe what happens to as many nutrients, both fuel and non-fuel, as you can.
3. What is the difference between anaerobic and aerobic metabolism? In what circumstances could anaerobic metabolism be important to the body?
4. Haematinic factors are those which are necessary for, and stimulate, the formation of red blood cells, including the haemoglobin they contain. What nutrients could be haematinic factors? (See also chapters 20, 21 and 22.)

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