Metabolic Regulation
A Human Perspective

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1. Some important concepts

1.1 Metabolic regulation in perspective

Appears to be a dull subject - learning the pathways, names, and structures. But in the physiological, whole organism context metabolism is relevant. We must obtain energy from the environment.

1.2 The chemistry of food and bodies

Macro and micronutrients
Energy sources - fuels

1.2.1 Some important chemical concepts
1.2.1.1 Polarity
   In a polar molecule the electrical charge is not uniformly distributed across the molecule.
   Hydrophobic compounds try to avoid water.
1.2.1.2 Osmosis
   Solvent, solute, membrane interactions and transports.
1.2.2 The chemical characteristics of macronutrients
1.2.2.1 Carbohydrates
   C\textsubscript{n} (H\textsubscript{2}O)\textsubscript{n}
   Monomers, dimers, polymers
1.2.2.2 Fats
   Lipid substances can be extracted using organic solvents.
   Saturated, unsaturated (monounsaturated, diunsaturated)
1.2.2.3 Proteins
   Polymers of amino acids

1.3 Some physiological concepts
1.3.1 Circulation, capillaries and interstitial fluid
   Blood circulates
   River system for transport
1.3.2 Blood, plasma and serum
   RBC - erythrocyte
1.3.3 Lymph and lymphatics
   Interstitial fluid

2. Digestion and intestinal absorption

Processes between food entering the mouth and its components appearing in the bloodstream.
2.1 The strategy of digestion

2.1.1 Carbohydrates
Complex, readily digestible
- Starch
  - Resistant starch in the small but not large intestine - semi-crystalline state
Complex, non-digestible
- Fiber

2.1.2 Fats
- Triacylglycerols
  - Need enzymes to break down

2.1.3 Protein and amino acids
- Proteins are converted to amino acids

2.2 Stages of digestion

2.2.1 The mouth
  - Cephalic phase
    - Brain anticipates - sight, smell, or thought
    - Saliva
      - Glycoprotein mucin lubricates
      - Lingual lipase

2.2.2 The stomach
  2.2.2.1 General description
  - 50 ml empty and expands to 1.5 liters
  2.2.2.2 Regulation of digestive processes in the stomach
    - Acetylcholine
    - Histamine
    - Gastrin
      - pH falls to 2 then inhibits gastrin release - feedback
  2.2.2.3 Digestive processes in the stomach
    - Acidic environment stops salivary amylase action
    - Most proteins are denatured in acids
    - The stomach is primarily an organ of mechanical digestion

2.2.3 The small intestine
  2.2.3.1 General description
    - Villi increase the surface area
    - Four sources of digestive agents
      - Gall bladder
      - Exocrine pancreas
      - Secretory cells
      - Brush-border membrane
  2.2.3.2 Regulation of digestive processes in the small intestine
    - Enterogastric reflex
    - Secretin
    - Cholecystokinin
    - Gastric inhibitory peptide
  2.2.3.3 Digestive processes in the small intestine
    - Starch - amylase
    - Protein - trypsin, chymotrypsin, carboxypeptidase
    - Lipid - pancreatic lipase

2.3 Absorption from the small intestine
  2.3.1 Monosaccharides
Enterocytes

2.3.2 Amino acids and peptides
- Free amino acids by specific transporters
- Peptide transporters

2.3.3 Lipids
- Fatty-acid binding protein
- Chylomicrons
- CAT

2.3.4 Other processes in the small intestine

2.4 Large intestine
- Absorbs water
- Bacterial activity

3. Metabolic characteristics of the organs and tissues

3.1 Metabolism of tissues and organs
- Glucose transporter properties

3.2 The liver
- Old Norse lifr. Having to do with the liver hepatic from Greek hepatos.

3.2.1 General description
- Adult human liver 1-1.5 kg with the hepatic artery supplying 20% of the blood and the portal vein. The absorbed materials from the intestine are brought in by the hepatic portal vein. The pancreatic veins bring the hormones glucagon and insulin. Their effect is exerted first on the liver. Numerous hepatic veins join the inferior vena cava which goes up toward the heart.
- The hepatic ducts carries bile from the liver to the gall bladder. Between 500 & 1000 ml of bile are produced daily. The bile duct carries the bile to the duodenum.
- Hepatocytes constitute 80% of the liver cells. There is metabolic zonation of hepatic metabolism; where the cells are located determines their function. The periportal hepatocytes on the outside are well oxygenated and supplied with substrates and are the sites of oxidative metabolism. They do gluconeogenesis. The perivenous hepatocytes with their interior location are more involved in glycolysis and ketone body production.

3.2.2 Liver metabolism
- Carbohydrates can be stored here.
  3.2.2.1 Carbohydrate metabolism
- Glucose whose concentration can reach almost 10 mM in the portal vein after a meal. Glucose is transported by GLUT2 transporter which is not insulin responsive catalyzes glucose uptake. Glucokinase catalyzes the phosphorylation to form glucose-6-phosphate. The glucagon/insulin ratio directs toward glucose metabolism or storage.
- Gluconeogenesis is regulated by rate of supply of substrates and the glucagon/insulin ratio.
  3.2.2.2. Fatty acid metabolism
- Beta-oxidation and storage as triacylglycerols are the major fates of fatty acids in the liver. Both mitochondrial and peroxisomal (5-30% total) both function. Ketone bodies can be produced and exported. OAA availability somewhat determines the partitioning between the citric acid cycle and ketone body formation.
Glucagon/insulin ratio controls the balance between FAO and esterification. Transport by
the carnitine palmitoyltransferase 1 is controlled by malonyl-CoA which is an inhibitor.
The liver makes bile salts and cholesterol.

3.2.2.3 Amino acid metabolism
Normally the body does not make either a net accumulation or loss of protein; it turns over, so oxidation must balance the rate of entry. The typical Western diet
provides 70 - 100 g of protein per day. The liver gets first shot at the amino acids and is the
only organ that can eliminate amino acid nitrogen by synthesis of urea. Amino acids don’t
provide the liver with energy but can be precursors for fatty acids, ketone bodies, and
 gluconeogenesis.

3.3 The brain
The brain is a heterogeneous organ with different patterns of metabolism. The
average brain weight 1.5 kg. It receives 750 ml/min of blood (50 ml/min/ 100 g) while
vigorous exercising muscle tissue receives blood at the same rate. The brain has a high rate
of metabolism. The brain oxidizes 120 g of glucose/day; 2 MJ or 20 % of the total for the
body.
There is a blood-brain barrier through which many compounds do not pass. The
brain as a whole does not use fatty acids as fuel and usually uses glucose. Ketone bodies
are used when starved.

3.4 Skeletal muscle
3.4.1 General description and structure of skeletal muscle
We have conscious control over these muscles. Creatine phosphate is a store
for ATP.

3.4.2 Metabolism of skeletal muscle: general features
Oxidative or red fibres have high content of myoglobin. White fibres lack
myoglobin and are anaerobic.

3.4.3 Routes of ATP generation in skeletal muscle
Glycogen, glucose and fatty acids are metabolized by the TCA cycle to yield
ATP.

3.4.3.1 Glucose metabolism
Glucose uptake is mediated by the insulin-sensitive GLUT 4.

3.4.3.2 Fatty acid metabolism

3.5 The heart
The myocardium is the muscular walls of the chambers. These muscles are
responsible for pumping the blood throughout the body. A myocardial infarction results
when some of the arteries supply blood to the heart are blocked and the corresponding
muscle cells are deprived of fuel and oxygen.
The heart engine can run on: non-esterified fatty acids, glucose, ketone bodies,
lactate. What it uses depends on what is available in the blood; after a meal when glucose is
high, the heart will mainly use glucose.

3.6 Adipose tissue
Several functions:
Cushioning - I know that since I lost weight chairs hurt more .
Thermal insulation - likewise, the cold brothers me more.
Storage of chemical energy in the form of triacylglycerols.

3.6.1 White and brown adipose tissue
Two types
Brown - multiple droplets
Can oxidize many substrates but unlike other tissues the ETC is
uncoupled. There is no ATP formation because thermogenin uncouples. Heat is liberated
Brown adipose is important in hibernating animals to help in the wakeup process. Surface area to mass relationship influences; greater surface area more heat loss.

3.6.2 White adipose tissue
In the adult human almost all of the adipose tissue is white. It functions in the regulated storage and release of fatty acids.

3.6.2.1 Triacylglycerol storage
The triacylglycerols are concentrated forms of energy storage because they are highly reduced. Triacylglycerols come from either the diet or from cellular synthesis. Triacylglycerols are carried in lipoprotein particles in the blood. Lipoprotein lipase functions to release the fatty acids. The lipoprotein lipase is exported from the adipocytes and functions in capillaries. The lipase associates with the endothelial cells via the complex glycoaminoglycan heparin sulfate via charge interactions. The released fatty acids diffuse through the interstitial space to the adipocytes where they are incorporated again into triacylglycerols.

Insulin stimulates lipoprotein lipase in a process that takes 3-4 h. Insulin also activates the de novo pathway.

3.6.2.1 Fat mobilization
When mobilized the released free fatty acids are carried bound to albumin. This release of fatty acids from the triacylglycerol is lipolysis and occurs via a hormone-sensitive intracellular lipase. This lipase is inactive when [insulin] is high and is activated by glucagon. Opposite effects of the two hormones; therefore, their ratio controls.

3.7 The kidneys
3.7.1 General description
Blood arrives via the renal arteries and is returned to the vena cava via the renal veins. The kidney is a filtering device which returns much of the water and solutes via reabsorption to the blood.

3.7.2 The scale of kidney function
About 1 liter of blood passes per minute which makes 800 liters each day. There is production of about 1-2 liters of urine per day. Some 180 g of glucose is reabsorbed per day.

3.7.3 Energy metabolism
Because of the high physiological activity in the kidney there is a high energy requirement. Some 10% of the total oxygen used at rest is utilized here. The cortex has a high rate of oxidative metabolism using glucose, fatty acids, and ketone bodies. The medulla carries out anaerobic glucose metabolism.

4. Some important endocrine organs and hormones

4.1 Endocrine glands and hormones
A gland is an organ that produces a secretion that enters the bloodstream for transport. Hormao is Greek for excite.

4.2 The pancreas
4.2.1 General description of the pancreas and its anatomy
It is 15-20 cm long and produces glucagon and insulin.

4.2.2 Insulin
Insulin is a peptide hormone consisting of two peptide chains, A, 21 amino acids; B, 30 amino acids. Preproinsulin has to be processed before becoming functional insulin. Insulin secretion is stimulated by glucose, amino acids, and weakly to ketone bodies. There are insulin receptors and insulin can be internalized where it is proteolytically degraded.

4.2.3 Glucagon
Glucagon is a single peptide chain of 29 amino acids. Its major action is to elevate blood glucose. There are glucagon receptors.

4.3 The pituitary gland
   It is able the size of a pea. It produces growth hormone, thyrotropin, prolactin, corticotropin, gonadotropins, vasopressin, and oxytocin.
   4.3.1 Hormones of the anterior pituitary
   Tropins are hormones that stimulate the production of other hormones. FSH is the follicle-stimulating hormone and luteinizing hormone are gonadotropins. Corticotropin (ACTH) is a 39 amino acid peptide that acts on the adrenal cortex. There is a 24-h circadian rhythm. Thyroid-stimulating hormone acts on the thyroid. Other hormones act on non-endocrine tissues: prolactin and growth hormone. Growth hormone is a 190 amino acid peptide hormone sometimes called somatotropin.
   4.3.2 Hormones of the posterior pituitary
   Oxytocin causes uterine contraction while vasopressin regulates urine production.

4.4 The thyroid gland
   It weights about 25 g and produces thyroglobulin and the thyroid hormones.

4.5 The adrenal gland
   4.5.1 The adrenal cortex: cortisol secretion
   Secretes steroid hormones many of which influence mineral metabolism and are known as mineralocorticoids.
   4.5.2 The adrenal medulla, adrenaline secretion and adrenaline action
   Adrenal hormones bring about an increase in metabolism.

5. Integration of carbohydrate, fat, and protein metabolism in the whole body

5.1 Carbohydrate metabolism
   Glucose is always present in the blood. But it not the same molecules. Elevation of glucose > 11 mM is harmful as is glucose < 3 mM
   Glucose enters the blood in three ways:
   1. Absorption from the intestine.
   1. Breakdown of glycogen in the liver.
   1. Gluconeogenesis in the liver.

   A typical western diet provide 300 g of carbohydrate per day. The amount in blood is about 25 mmole or 4.5 g. Even a single meal gives us more carbohydrate than that carried in the blood.
   5.1.1 The post-absorptive state
   After the last meal absorbed the glucose comes almost exclusively from the liver.
   The liver gets in mg/min 10 of ala, 30 of lactate, and 10 of glycerol. It ships out that 50 plus 80 from glycogen stores giving 130 into the blood stream. The brain takes 80 (120 g/day and converts it to carbon dioxide).
   5.1.2 Breakfast
   Most dramatic switch from hungry to full. See increase in blood glucose in about 15 min and that peaks around 60 min with a moderate breakfast.
   5.1.2.1 Carbohydrate metabolism in the liver after breakfast
   The liver sees the largest change in [glucose]. Switches from glycogen breakdown to glycogen storage when supplied with glucose and the increase in the insulin/glucagon ratio. No glucose is exported until the level of blood glucose falls.
   5.1.2.2. Carbohydrate metabolism in other tissues after breakfast
Other tissues respond to the increase insulin concentration.

### 5.1.2.3 Disposal of glucose after a meal
Within 5 h after a meal approx. 25 g of the 100 g carbohydrate ingested will have been stored and 75 g oxidized.

### 5.2 Fat metabolism
Non-esterified fatty acids turn over rapidly. Other forms may last several hours or days. The [fat] in blood varies widely.

#### 5.2.1 Plasma non-esterified fatty acids
Non-esterified fatty acids come only from adipose tissue via the hormone-sensitive lipase. Non-esterified fatty acids are not water soluble and must be transported via plasma serum albumin. The plasma non-esterified fatty acids vary inversely with plasma glucose and insulin.

#### 5.2.2 Plasma triacylglycerol
Triacylglycerol is water-insoluble and is carried by lipoprotein structures.

#### 5.2.3 The post-absorptive state
After an overnight fast the non-esterified fatty acids in plasma is about [0.5 mM] and the total triacylglycerol [1 mM].

#### 5.2.4 Breakfast
What happens after eating fried bacon and eggs?

#### 5.2.4.1. Non-essential fatty acid metabolism after breakfast
Increasing insulin ip esersono tclu gseocrinseapesus eprs se hemtorhe-onnsevstiilie sepaT e.ehrs it opnomectleup ssrenpios .T eh erelsao fonne-ssreiifdef att ycaisdf orma idops eitsu esia lomtsc opmeletl yhstu-odnw . fAet r35-h t h eniuslnic nocnerttainob geisnt odceilen na dhter sertani tno af tomblizitainoi srtlexade.

#### 5.3.1.1 Essential and non-essential amino acids, and other metabolically distinct groups of amino acids

- **Essential:**
- **Non-essential**
  - A, D, N, C, E, Q, G, P, S, & Y

#### 5.3.2 Branched-chain amino acids and muscle amino acid metabolism
The branched chain $\alpha$-keto acid dehydrogenases are important in degradation.

5.3.2.3 Alanine and glutamine

Have special places in amino acid metabolism. They predominate the amino acids leaving muscle. $Q$ serves to transport nitrogen. Alanine is addressed to the liver, while glutamine goes to the small intestine and the kidney.

5.3.3 The overall control of protein synthesis and breakdown

Two hormones stimulate net protein synthesis: insulin and growth hormone.

5.4 Links between carbohydrate, fat, and amino acid metabolism

5.4.1 Carbohydrate and fat metabolism

5.4.1.1 Lipogenesis

The synthesis of lipid. Occurs in liver and adipose tissue. Fatty acids are made from acetyl-CoA and the pathway is stimulated by insulin through activation of acetyl-CoA carboxylase. The supply of substrate prevents futile cycling; insulin retards fat mobilization.

5.4.1.2 Metabolic interactions between fatty acids and glucose: the glucose-fatty acid cycle

Glucose $\leftrightarrow$ fatty acid cycle is not a metabolic cycle but is a regulatory connection.

5.4.2 Interactions between carbohydrates and amino acid metabolism: the glucose-alanine cycle and gluconeogenesis from amino acids

Alanine is pyruvate is a disguise. Cori cycle of glucose-lactate is similar to the glucose-alanine cycle.

5.5 An integrated view of metabolism: a metabolic diary

5.5.1 The post-absorptive state: waking up

Plasma glucose and insulin are at their lowest and non-esterified fatty acid levels are at their highest. Glucose comes from breakdown of glycogen and gluconeogenesis.

5.5.2 Breakfast goes down

A lazy day (not much exercise)

Glucose and amino acids are in the blood stream and available in 15-30 min. After a good meal the blood glucose will remain elevated 3-4 h. Release of non-esterified fatty acids decreases. Switch to glucose metabolism. Store excess.

5.5.3 Another meal follows

Time to eat again and there has been no exercise. More substrates to store.

5.5.4 An energetic day

Widely spaced meals with exercise. If a healthy breakfast, then less to store. Sharp peak of glucose in the blood. Use some of the fuel for exercise rather than store. Then a low-fat lunch still not much to store. An afternoon walk leads to energy utilization. Less stored and more oxidized = health.

5.6 Recap: metabolic control in a physiological setting

Not on/off switch, but reostat.

6. The nervous system and metabolism

6.1 Outline of the nervous system as it relates to metabolism

6.1.1 The nerve cell

AKA neurons. They may be long and don’t divide. They have a high rate of glucose metabolism and require oxygen. If deprived of oxygen for more than a few minutes, they die. They communicate via chemical synapses that release neurotransmitters. Acetylcholine and noradrenaline are often used.
6.1.2 The wiring diagram
CNS is the brain and spinal cord. The rest is the peripheral nervous system.

6.2 Basic physiology of the nervous system
6.2.1 The brain
Has many cell types and has a high rate of blood flow thus nutrient supply.
Glial cells provide mechanical support and electrical insulation - they are 90% of the total.
6.2.1.1 The hypothalamus
An integrating center. Need 4-5 mM glucose and it maintains.
6.2.1.2 The cerebellum and brain stem
Movement

6.2.2 The autonomic nervous system
6.2.2.1 The sympathetic nervous system
Bundles are sympathetic trunks.
6.2.2.2 The parasympathetic nervous system
Uses acetylcholine.
6.2.2.3 The somatic nervous system

6.2.3 Neurotransmitters and receptors
6.2.3.1 Adrenergic transmission
6.2.3.2 Cholinergic transmission

6.3 Major effects of adrenergic stimulation
6.3.1 Stimuli for activation of the sympathetic nervous system and adrenal medulla
6.3.2 Circulatory effects of adrenergic activation
6.3.3 Metabolic effects of catecholamine
   In the liver, catecholamines stimulate glycogen breakdown. In skeletal muscle, the catecholamines are insufficient by themselves to activate glycogenolysis.
6.3.3.1 Glycogenolysis
6.3.3.2 Lipolysis

6.4 Effects of the autonomic nervous system on hormone secretion

6.5 Summary
   May have a direct influence on metabolism
   The effects may be mediated by hormones
   Via others systems such as the circulatory.

7. Coping with some extreme situations

7.1 Situations in which the body needs to call on its fuel stores
   911 calls .. emergencies .. respond .. help .. stress

7.2 The body’s fuel stores
   7.2.1 Carbohydrate
      Free glucose amount is small. Can support the brain for two hours. But that won’t keep us alive overnight. Thus we must have some carbohydrate stores. Glycogen is it. The liver and muscle have it and the glycogen will supply for 24 h.
   7.2.2 Fat
      Fats stores are generally 1-2 orders of magnitude greater. We store energy for about 50 days. When fats are used over the long term, metabolism switches to ketone bodies.
   7.2.3 Amino acids
There are no particular storage forms of amino acids. The structural/catalytic proteins can be degraded to give us a 21 day supply of energy.

7.3 Starvation

Brain fuel

- 0-4 h, exogenous glucose - I
- 4-12 h, glucose from glycogen - II
- 12-30 h, glucose via gluconeogenesis - III
- 2-24 days, glucose and ketone bodies - IV
- 24-40 days, ketone bodies and glucose - V

7.3.1 The early phase

Ketogenesis increases

7.3.2 The period of adaptation to starvation

- Gluconeogenesis is stimulated
- Lipolysis then use glycerol for glucose synthesis
- Metabolic rate falls
- Ketone bodies preferred

7.3.2.1 Hormonal changes

Thyroid hormone falls

7.3.2.2 Adaptation of fatty acid, ketone body, and glucose metabolism

7.3.2.3 Sparing of muscle protein

7.3.2.4 Kidney metabolism

7.3.3 The period of adapted starvation

Adapted in three weeks.

7.4 Exercise

7.4.1 Types of exercise

- Anaerobic
- Aerobic

7.4.2 Intensity of exercise

- Force - that which tends to cause a body to accelerate
- Work - product of distance moved and the force exerted
- Energy - capacity to do work
- Power - rate of doing work

7.4.3 Metabolic regulation during anaerobic exercise

- Increase glycolytic flux

ActivityEnergy expenditure, METResting1Sleeping9Light housework (sweeping)2.5Heavy housework (washing car)4.5Walking (3 mi/h)3.5Dancing3-7Swimming6-11Jogging10-12Squash12Marathon running18

One MET is the normal metabolic resting rate; about 4.8 kJ/min man and 3.8 kJ/min woman of average sizes

7.4.4 Metabolic regulation during aerobic exercise

- Many forms combine both
- 100 m sprint is anaerobic
- 400 m is a combination
- 42.2 km marathon is almost purely aerobic

7.4.5 Nervous system and cardiovascular responses during aerobic exercise

- Somatic supplies the impulse for the muscles to act
- Need both contraction and activation of glycogen breakdown

7.4.6 Other hormonal responses during aerobic exercise
Distribution of blood flow, %
Organ
Rest, 5 liters/min
Heavy work, 25 liters/min
Lungs, 100
Intestines, 20-25
Heart, 5-4
Kidneys, 2-4
Bone, 3-5
Brain, 5-1
Skin, 5
Muscle, 15-20

7.4.7 Carbohydrate metabolism during endurance exercise
Blood glucose supports just a few minutes of exercise
Liver glycogen less than an hour
9. Diabetes mellitus

9.1 Different types of diabetes

9.2 History of the study of diabetes and clinical features
   9.2.1 History of diabetes
      1500 BC
      1869 islets of Langerhans
      1889 removal of pancreas led to diabetes (Minkowski & von Mering)
   9.2.2 Insulin-dependent diabetes mellitus
      Destruction of insulin producing cells
   9.2.3 Non-insulin-dependent diabetes mellitus
      Insulin is less effective

9.3 Alterations in metabolism in diabetes mellitus
   It is a mistake to think that people who have diabetes and are treated are free from problems. They rarely die from lack of insulin but their life expectancy is reduced and their quality of life may be reduced due to the complications. That is something that I had to accept; I am not sure that my wife realizes it because I keep the blood glucose under fairly good control.
   9.3.1 Untreated IDDM
      Catabolic - breakdown of fuel stores and tissues.
   9.3.2 Metabolic alterations in NIDDM
      If you don’t take care, the blood glucose concentration just increases through the day.

9.4 Treatment of diabetes mellitus
   9.4.1 IDDM
      Must treat with insulin
   9.4.2 NIDDM
      Diet and exercise
      Diet, exercise, and medication

9.5 Longer-term complications of diabetes
   Vascular disease
   Nephropathy
   Neuropathy
   Retinopathy

10. Energy balance and body weight regulation

10.1 Energy balance
   Energy can neither be created nor destroyed but can be interconverted between different forms. The human body is a chemical device that takes in chemical energy and converts it by controlled oxidation into other forms of energy (stored compounds) and into mechanical work and heat.

   \[ \text{Energy intake (food)} = \text{Energy expended (heat, work, biosynthesis)} + \text{Energy stored} \]

   If you don’t use it, you store it. The storage of larger excesses is in your fat closet.
10.2 Energy expenditure
   10.2.1 Measurement of energy expenditure
   10.2.2 The components of energy expenditure

10.3 Obesity
   10.3.1 Definition of obesity
       Body mass index or Quetelet’s index; skinfold thickness
   10.3.2 How does obesity develop?
       1. An elevated rate of input
       2. A decreased rate of energy expenditure
          Can make the job of losing difficult
          But most obese individual have a higher metabolic rate.
          Therefore the trouble is 1 - too great an intake
   10.3.3 Health implications of obesity
   10.3.4 Metabolic changes in obesity

10.4 Dieting and metabolic regulation
   10.4.1 Dieting as a battle against adaptation
   10.4.2 Quantitative aspects of dieting
   10.4.3 Alternative to rapid dieting
   10.4.4 Modification of energy expenditure