Metabolism – The sum of all physical and chemical processes by which living, organized substance is produced and maintained.

Dorland’s Medical Dictionary

Greek

Metaballein – to turn about, change, alter

Homeostasis

Stability in the normal body states of the organism
Simple unicellular organisms such as protozoa and bacteria are pleuripotential, containing all the metabolic machinery to maintain homeostasis.

Cells of complex organisms such as mammals are specialized to perform specific inter-related functions so that maintenance of homeostasis relies on the cells, tissues, and organs of the body working together.

What are the causes of metabolic disease?

1. Genetic
2. Faulty nutrition
3. Hormonal imbalances
4. Drugs / pharmaceuticals
5. Toxicities
6. Microorganisms
These various causes can disrupt specific metabolic pathways or can cause damage to specific organs or tissues leading to secondary metabolic disease.

Examples:
- **Copper deficiency** – cytochrome oxidase
- **Aflatoxin** – liver damage leading to hepatic encephalopathy

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**Genetic Basis of Metabolic Disease**

- Hereditary defects constitute the largest and most diverse category leading to metabolic disease.
- Many of these relate to faulty synthesis or deficiency of enzymes involved in metabolic pathways – Example = pyruvate kinase deficiency in red blood cells, an enzyme in the glycolytic cycle.

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**Nutritional Basis of Metabolic Disease**

- Faulty nutrition can deprive the body of important nutrients necessary for normal metabolic functions:
  - Vitamins and minerals as co-factors for many enzymes
  - Deficient glucose (carbohydrates) for normal energy metabolism
  - Deficient protein - kwashiorkor
Hormonal Basis of Metabolic Disease

- Hormones participate in many metabolic processes in diverse tissues, cells, and organs
  - Diabetes mellitus: insulin
  - Hyperparathyroidism: parathormone
  - Addison's disease: aldosterone

Pharmaceutical Basis of Metabolic Disease

- Many drugs and pharmaceuticals inhibit enzymes or otherwise block important biochemical pathways. Drugs may have undesirable secondary effects.
  - **Cortisone**: inhibits the enzyme phospholipase A₂ blocking synthesis of prostaglandins and leukotrienes formed from lipoic acid in the cell membrane
  - **Lasix (furosemide)**: blocks resorption of sodium (and H₂O) from kidney tubules

Toxic Basis of Metabolic Disease

- The action of many poisons is to disrupt metabolic pathways or to damage tissues leading to secondary metabolic disease
  - **Organophosphates**: Inhibit cholinesterase enzymes leading to persistent neural stimulation
  - **Excess iodine**: Interferes with thyroid hormone synthesis leading to hypothyroidism and secondary metabolic disease
Infectious Basis of Metabolic Disease

• Primary or secondary effects on normal metabolism
  – Parvovirus: Vomiting and diarrhea leading to dehydration, ionic imbalances, and acid-base disturbances
  – Toxigenic bacterial infections: Strains of *E. coli* producing secretory diarrhea

This lecture is meant to give a brief overview of metabolic disease.

The remainder of this lecture will cover a few of the metabolic diseases.

Acid – Base Disturbances

Disturbances in pH can contribute to morbidity and mortality in a variety of disease states.
Disturbances in acid-base balance
Acidosis and Alkalosis

- pH in the body is a reflection of the H⁺ concentration
- Maintenance of pH in the body fluids is critical for normal homeostasis
- Deviations from normal can affect many biochemical (enzyme catalyzed) reactions

Normal pH in dogs is approximately 7.4
- pHs of 6.9 and 7.8 represent the life-threatening extremes
- Buffer systems in the body help regulate pH

Buffer Systems
- Hemoglobin in red blood cells
- Proteins / phosphates – contain weak acidic and basic structural groups
  - The protein matrix of bone is a powerful buffering system
- Bicarbonate buffering system (lung & kidney)
  \[ \text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^- \]
Respiratory Acidosis

\[
\text{CO}_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-
\]

Lung

- If the lung fails to remove CO\(_2\), acidosis can occur.

Kidney

Renal Compensation:
- Excretion of H\(^+\)
- Production and resorption of HCO\(_3^-\)

Respiratory Alkalosis

\[
\text{CO}_2 + H_2O \leftarrow H_2CO_3 \leftarrow H^+ + HCO_3^-
\]

Lung

- If the lung removes too much CO\(_2\), alkalosis can occur.

Kidney

Renal Compensation:
- Resorption of H\(^+\)
- Excretion of HCO\(_3^-\)

Causes of respiratory alkalosis
- Hyperventilation:
  - Anxiety, fever, pain, high ambient temperature, CNS disease

Metabolic Acidosis

- **Causes**
  - Lactic acidosis (hypoxia, ischemia)
  - Ketoacidosis (diabetes mellitus – production of acetoacetic and hydroxybutyric acid from fatty acid precursors)
  - Severe diarrhea with loss of bicarbonate
  - Kidney disease – failure to excrete H\(^+\) conserve HCO\(_3^-\)
- **Pulmonary Compensation**
  - Hyperventilation
- **Renal Compensation**
  - Excretion of H\(^+\) and conservation of HCO\(_3^-\)
**Metabolic Alkalosis**

- **Causes**
  - Vomiting w/ loss of HCl
  - Diuretics
- **Pulmonary compensation**
  - Decreased respiratory rate
- **Renal compensation**
  - Both associated with fluid volume depletion
  - The kidney retains Na⁺ at the expense of H⁺, restoring fluid volume
  - Once volume is restored, the kidney can conserve H⁺

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**Hepatic Encephalopathy**

It is well recognized that liver failure can secondarily affect normal brain function.

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**The Liver – basic functions**

- Filter blood and eliminate substances including bi-products of normal metabolism that are potentially harmful
- Amino acid and protein synthesis
- Fatty acid metabolism
- Glycogen production, storage, and glucose production (gluconeogenesis)
- Storage of nutrients (Vitamin A)
- Digestion of nutrients (bile)
Encephalopathy can result from various types of liver injury – immaturity

Kernicterus

Encephalopathy can result from various types of liver injury – altered blood supply

Encephalopathy can result from various types of liver injury – massive necrosis
Encephalopathy can result from various types of liver injury – chronic disease

Potential causes of the encephalopathy

- **Ammonia (NH₃)** – ammonia is increased in most cases because the failing liver cannot complete conversion to urea
- In the brain, the enzyme that metabolizes or detoxifies ammonia is glutamine synthetase
  \[ \text{glutamate} + \text{NH}_3 \rightarrow \text{glutamine} \]
- It is believed that excessive glutamine synthesis leads to (among others):
  - Altered glutamate for excitatory neurotransmission
  - Osmotic burden leading to edema and brain swelling

Diabetes mellitus
Diabetes mellitus

- One of the most common endocrine-related metabolic diseases in dogs and cats and in humans (in the top ten leading causes of death)
- The disease is due to either deficient production of INSULIN by pancreatic islets and/or resistance of the peripheral tissues to the action of insulin

Functions of insulin

- Stimulates uptake of glucose into most cells (brain, renal tubular epithelium, and RBCs do not require insulin)
- Enhances intracellular glucose metabolism
- Increases glycogenesis
- Increases amino acid uptake and protein synthesis
- Stimulates lipogenesis
- Decreases fatty acid utilization (lipolysis) and gluconeogenesis

Diabetes Mellitus

Persistent hyperglycemia (too much glucose in the blood) is the sine qua non of diabetes mellitus
Classification of Diabetes in Humans

- Type 1
  - Also called insulin dependent or juvenile diabetes mellitus
  - There is an absolute deficiency of insulin
  - Genetics, environment, autoimmunity
- Type 2
  - Non-insulin dependent or adult onset
  - No absolute deficiency of insulin
  - Peripheral tissues are resistant to the action of insulin

Metabolic dysfunction and complications of diabetes mellitus

- Dehydration – mechanism?
- Ketoacidosis – occurs with type 1 diabetes.
- Nonketotic hyperosmolar coma – related to osmotic diuresis due to glucosuria + dehydration in elderly diabetics – type 2
- Nonenzymatic glycosylation of proteins due to persistent hyperglycemia
- Alternate metabolic pathways (polyol pathway) for glucose metabolism

Protein glycosylation

- Irreversible glycosylation of long-lived poorly degradable proteins (AGEs) such as collagens that accumulate over time in the interstitium and blood vessel walls contributing to:
  - Diabetic angiopathy
  - Glomerulonephropathy
  - etc
Protein glycosylation

• AGEs bind to receptors on a variety of cell types (endothelium, monocytes-macrophages, lymphocytes, renal glomeruli)
  – Monocyte chemotaxis
  – Release of cytokines and growth factors
  – Increased endothelial permeability
  – Increased procoagulant activity
  – Increased synthesis of extracellular matrix proteins

• AGEs can damage cells/tissues directly
  – Treatment with aminoguanidine, an agent that prevents AGE formation helps to prevent
    • Angiopathy
    • Neuropathy
    • Retinopathy
    • Nephropathy

Diabetic glomerulonephropathy
(Kimmelstiel-Wilson bodies)

Increased intracellular glucose in non-insulin dependent cells

• Nerves, lens, kidney, etc
• Excess glucose is metabolized to sorbitol & fructose via the enzyme aldose reductase
  – Increased osmolarity → cell swelling
  – Decreased phosphoinositide metabolism
  – Decreased diacylglycerol, protein kinase C, and Na+-K+ ATPase activity
Sample Question #1

- Which of the following is true concerning the regulation of pH in the body?
  1. The proteinaceous matrix of bone is a weak buffer
  2. In acidosis, the kidney eliminates bicarbonate in the urine and retains H+
  3. A response of the lung to metabolic acidosis is increased respiratory rate
  4. The renal response to metabolic alkalosis occurs within minutes

Sample Question #2

Briefly describe what is meant by the term hepatic encephalopathy.