CLINICAL BIOCHEMISTRY (2002)

METABOLIC PATHWAYS

Students are requested to demonstrate the knowledge of the following metabolic pathways:
Glycolysis/gluconeogenesis
Tricarboxylic acid cycle
Pentose phosphate shunt
Respiratory chain
Heme synthesis
Cholesterol synthesis (farnesyl, geranyl)
Sketch of AA metabolism (essential, chetogenetic, gluconeogenetic)
Urea synthesis, transaminases

Knowledge doesn't include the ability to draw formulas of the single molecules involved in the pathway but:
Starting molecules and their source (diet, blood, specific organs, etc)
Final products and their release (CO_2, urea, lactate etc.)
By products: ATP, NADH, NADPH and their possible use (e.g. NADPH: fatty acid synthesis, deoxy ribonucleotides etc.)
Mechanism of the in/out movement of molecules from the cells (pumps, antiports, simports, etc.)
Nutrients: oxygen, fatty acids, glucose, AA.
Cofactors: vitamin and metal ions
List of all the molecules involved in every metabolic pathway (e.g. glycolysis: glucose, ATP, NAD, phosphate, Mg)
Role of enzymes: they increase the reaction rate, not the direction. The direction of a chemical reaction depends on $?G_0$ and ?G (local concentration of substrates).

THE LIVING CELL

To better understand their real role in the cell life the metabolic pathways have to be fitted into the description of the living cell . All life forms in our environment share some properties and can be described as:
Dissipative: life takes place only in environments with an excess of energy: in our case, in the sunlight.
This concept includes the following facts:

- ?? Cells have to feed continuously
- ?? Cells have to breath continuously
- ?? Cells cannot ever stop producing energy
- ?? Cells use energy to keep many ionic gradients (Ca++, Na+, K+, Cl- etc.)

Gradients are necessary for most cell functions (signal transduction, glucose and AA transport, etc.)
Evolutionary: formation of evolutionary trees for any molecule and organism mediated by irreversible bifurcation followed by selection. The driving forces of bifurcation and selection depend on the environment and can be considered "local".
Cyclic: at any level from the molecules to the species, precise feedback mechanisms can be identified that regulate the number of the objects involved in the equilibrium.

Oscillating: in any self-regulatory cyclic system the number of any item is changing in time with a periodicity that depends on the size of the system – from seconds for chemical reactions to years for prey/predator relationships – and the time the feedback signals need to diffuse across the system.
Competitive: as biological systems tend to expand exponentially in a finite environment, they become – sooner or later – limited in their growth due to a shortage in some essential factor ("nutrient"). The competition for the limiting nutrient will locally drive the selection.
Concept of "essential" nutrient
Metal ions (Zn, Cu, Fe, Se)
Inorganic phosphate
Selected aminoacids
Vitamins (why eating vitamins is better than producing them by themselves)

SIGNAL TRANSDUCTION (ST)

Definition of Sign and Signal

We call signals all (physical or chemical) events able to transmit information to a cell. Signaling requires at least two components:

- a physical (e.g. sound) or chemical (e.g. hormone) event that it is released into the environment in specific conditions and that we can call a sign (S)
- a cellular structure able to react with (S) modifying the cell behavior according to the concentration and direction of (S). These structures are called Receptors (R).

$(S)_n$ are classified as sound, light, hormones, cytokines, chemokines, growth factors, and so on, according to their major effect, but they share a common property: the ability to give information about the existence of specific environments or about the availability of one or more nutrients. The minimal information content carried by any sign is that all the conditions required for its synthesis are present. But also Receptors (R) are synthesized in specific conditions and therefore carry the information that this conditions exist.
To make signal understandable to the cell a set of chemical events called signal transduction take place upon binding of the ligand (S) to its receptor.
Non-linearity of signal transduction: ST is a multi-step process with different checkpoints sensitive to different external factors (inositol ✍ NADH/NAD+ ✍ ethanol; oxygen, diet, G-proteis and miristoyl and farnesyl, etc)

Difference between nutrients and signals

Nutrients are required for a chemical reactions (substrates or cofactors) whose rate is dependent on their presence
Signals regulate the reaction rate giving (how???) some information concerning the availability of nutrients (T3/T4 ✍ oxygen, insulin ✍ glucose etc.)

As a matter of fact the whole metabolism is always and only (???) regulated by its own substrates either directly or through signals.