CELLULAR RESPIRATION

A series of enzyme catalysed reactions in cells during which the chemical-bond energy of complex organic substances is released and converted into the usable form called **adenosine triphosphate (ATP).**

Storage Of Chemical Energy In Organic Substances (Food)

The C-H covalent bonds in organic substances (e.g. carbohydrates and lipids) form by sharing pairs of fast-moving energetic electrons, and therefore contain potential energy. The catalytic breakage of the C-H bonds releases energy, some of which powers the formation of ATP – a compound that can readily hydrolyse to provide energy that powers cellular activities. **The higher the C-H bonds, the more the energy yields. This explains why lipids yield twice more energy than carbohydrates of same mass.**

The Fate Of High Energy Electrons And Hydrogen Ions Released From Breaking C-H Bonds

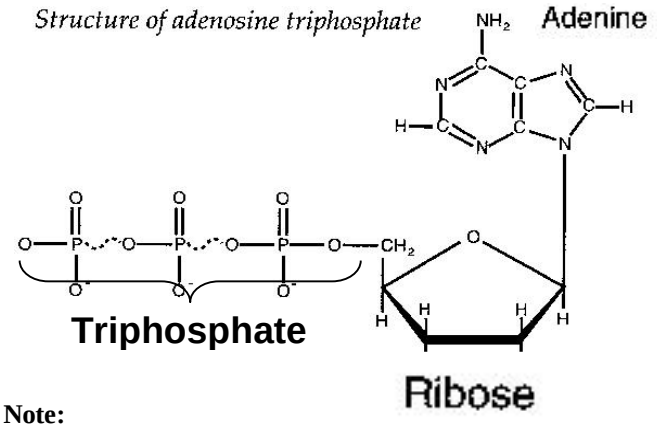
To avoid fatality, the electrons lost from compounds are prevented from joining other molecules by joining electron carrier molecules which pass them along the **electron transport chain** until they get attached to oxygen, which becomes negatively charged, O^{2-}. As the electrons are transferred along the transport chain, energy is gradually extracted from them to power ATP formation. To avoid PH becoming acidic, which would be fatal, hydrogen ions, H^{+} combine with O^{2-} to form neutral water.

ADENOSINE TRIPHOSPHATE (ATP)

ATP is a compound made up of a molecule of **adenine** – a nitrogenous base, a molecule of **ribose sugar**, and **three phosphate molecules**.

ATP is an energy carrier because it stores chemical energy, which is released as free energy on hydrolysis of the covalent phosphate to phosphate bonds. Hydrolysis of ATP to form **adenosine diphosphate (ADP)** releases 30.6kJmol^{-1} of free energy, and further hydrolysis of the terminal phosphate bond of ADP to form **adenosine monophosphate (AMP)** yields another 30.6kJmol^{-1} of free energy, but hydrolysis of the phosphate-ribose bond in AMP releases very little energy.

*(**Suzan and Glenn Toole 1997**: advanced human and social biology, student's art notebook pg.66)*



Note:

(1) Phosphorylation of AMP (addition of phosphate molecules to AMP) forms ADP, while Phosphorylation of ADP yields ATP.

(2) The addition of each phosphate molecule requires 30.6kJ, and therefore energy released from any chemical reaction if less than 30.6kJ cannot be stored as ATP but is lost as heat.

(3) High-energy bonds are symbolized by the **squiggle (~)** i.e. solid curved line.

(4) Potential energy increases whenever things experiencing a repulsive force are pushed together such as adding the 3rd phosphate to an ADP molecule. Potential energy also increases whenever things that attract each other are pulled apart as in the separating of protons from the electrons.

HOW IS ATP FORMED IN CELLS?

1. Directly by **substrate-level Phosphorylation** i.e. direct transfer of a phosphate group from high energy phosphorylated compounds to ADP. E.g. **Phosphoenolpyruvate, 1, 3-Bisphosphoglycerate, acetyl phosphate and phosphocreatine.**

2. Indirectly by use of energy supplied by transmembrane proton concentration gradients e.g. **oxidative Phosphorylation** in the mitochondria and **photophosphorylation** at the thylakoid membranes of chloroplasts during photosynthesis.

WHY ATP IS REFERRED TO AS "THE UNIVERSAL ENERGY CURRENCY"
It is because ATP's structure as the energy supplier molecule is the same in all living organisms.

USES OF ENERGY OF ATP IN CELLS:
(1) Enables transport of materials like in the phloem and xylem of plants
(2) Enables movement of cilia, flagella and muscle contraction
(3) Allows active transport to be carried out (movement of substances against concentration gradient) e.g. ion pumps
(4) Drives endergonic reactions e.g. assembly of amino acids into proteins, synthesis of polysaccharides from monosaccharides, and DNA replication
(5) Activates chemicals to become more reactive e.g. Phosphorylation of sugar during Glycolysis
(6) Enables formation of vesicles during secretion of cell products.

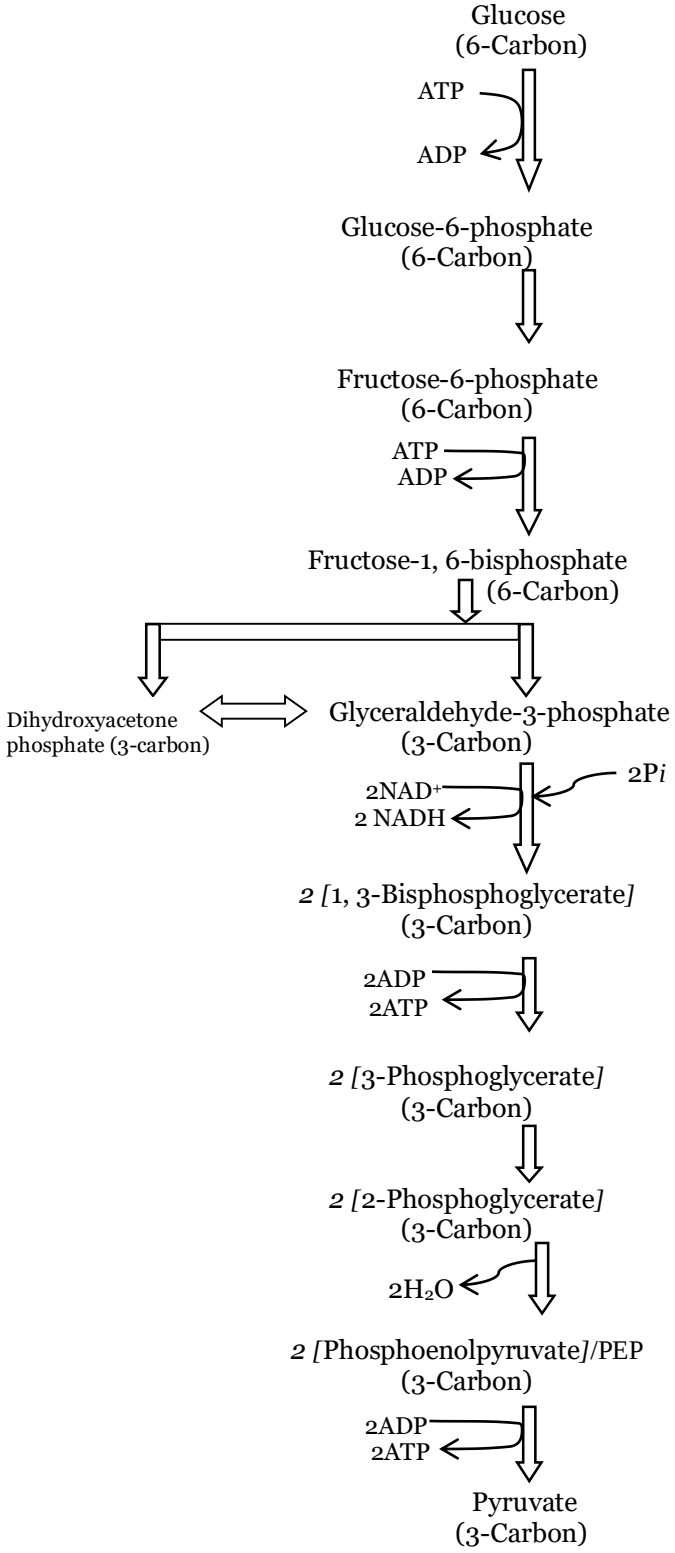
SITE OF RESPIRATION IN CELLS

Cell type	Location of pathway in cell
All prokaryotic cells	Infoldings of cell membrane (mesosomes) and in cytoplasm
All eukaryotic cells	Cytoplasm, matrix and inner membranes of mitochondria

STAGES OF CELLULAR RESPIRATION
(1) Glycolysis
(2) The link reaction (linking glycolysis to Krebs cycle)
(3) Krebs cycle
(4) Electron transfer system
Each stage is part of the whole process.

GLYCOLYSIS (*glyco* = carbohydrate; *lys* = splitting; *sis* = the process of)
Definition:
A series of enzymatically controlled reactions in the cytoplasm of cells during which one molecule of a six-carbon sugar glucose, is split into two molecules of the three-carbon compound Pyruvate, with a net output of two ATP molecules.

DESCRIPTION OF THE PROCESS OF GLYCOLYSIS



Glycolysis starts with phosphorylation of glucose by ATP to form glucose-6-phosphate. This process **(1)** chemically reactivates glucose **(2)** traps glucose in the cell because the phosphate group bears a negative charge yet the cell membrane is impermeable to ions.

Glucose-6-phosphate isomerizes to form fructose-6-phosphate to ease another Phosphorylation.

Fructose-6-phosphate is further activated by another phosphorylation by ATP to form fructose-1, 6-bisphosphate ***(OLD NAME: fructose-1, 6-diphosphate)***

Fructose-1, 6-bisphosphate splits at once into **glyceraldehyde-3-phosphate** (3-phosphoglyceraldehyde/3-PGAL) and its isomer **dihydroxyacetone phosphate.** Dihydroxyacetone phosphate isomerises into **glyceraldehyde-3-phosphate**

Each 3-PGAL is dehydrogenated by nicotinamide adenine dinucleotide (NAD^+) to form reduced nicotinamide adenine dinucleotides (NADH) Each 3-PGAL molecule is phosphorylated by phosphates present in the cytoplasm to form 1, 3-bisphosphoglycerate, which later donates the phosphate to ADP to form ATP and 3-phosphoglycerate, which has 3-carbons.

Each 3-phosphoglycerate isomerizes to form 2-phosphoglycerate,

Each 2-phosphoglycerate loses a water molecule to form 3-phosphoenolpyruvate (PEP).

Each 3-phosphoenolpyruvate (PEP) loses a phosphate to ADP to form ATP and pyruvate which has three-carbons

SIGNIFICANCE OF GLYCOLYSIS

Glycolysis forms a net of:
(1) 2 ATPs used to power cell activities
(2) 2 NADH and Pyruvate which may be further oxidized to generate additional ATP. However in oxygen deficiency, both NADH and pyruvate undergo fermentation to regenerate NAD^+.

THE FATE OF PYRUVATE, NADH AND ATP PRODUCED FROM GLYCOLYSIS

1. ATP:

It is hydrolysed to release energy to power the cell's needs.

2. NADH:

Under aerobic conditions (in the presence of oxygen), NADH is converted into $FADH_2$ which is then shuttled into the mitochondria where it donates electrons to a series of electron carriers until they reach the final oxidizing agent oxygen in a process called electron transport system. During this process, the free energy of electron transport drives the synthesis of ATP from ADP and NAD+ is regenerated such that it can participate in further catalysis.

Under anaerobic conditions, NADH must be re-oxidised by other means in order to keep the glycolytic pathway supplied with NAD+

3. PYRUVATE:

Under **aerobic conditions**, it is completely oxidised via the **citric acid cycle** to carbondioxide and water.

Under **anaerobic conditions** in the cytoplasm, pyruvate under goes **fermentation**.

Types of fermentation

There are many types of fermentation, but the two common types are given below:

(a) Alcoholic fermentation: pyruvate is decarboxylated to yield carbondioxide which is converted to a 2-carbon compound **acetaldehyde**. Acetaldehyde is then reduced by NADH to **ethanol** and NAD+ also forms. NAD+ enables the continuation of glycolysis. Alcoholic fermentation occurs in some **bacteria** and **yeasts.**

(b) Lactic acid fermentation: pyruvate is reduced directly by NADH to form **lactic acid** as the end product. No carbondioxide is released. Lactic acid fermentation **(1)** is carried out by certain fungi and bacteria during the formation of yoghurt and cheese **(2)** occurs during oxygen scarcity in human skeletal muscle cells during sprinting. The lactic acid is gradually carried away by blood to the liver and converted back to pyruvate by liver cells.

If ATP is abundant, pyruvate and lactate can be used as a substrate in the synthesis of glucose.

Comparison of cellular respiration and fermentation

Similarities: Both **(1)** form ATP **(2)** use glycolysis to oxidise glucose to pyruvate **(3)** use NAD+ as the oxidizing agent that accepts electrons from food during glycolysis **(4)** may be carried out by same cells (e.g. muscle cells) or same organisms (e.g. yeasts and bacteria).

Differences:

Cellular respiration	Fermentation
• Final electron acceptor from is oxygen	• Final electron acceptor is an organic molecule such as pyruvate (lactic acid fermentation) or acetaldehyde (alcohol fermentation)
• Harvests much more energy from each glucose molecule i.e. up to 38 ATP per glucose molecule.	• Harvests much less energy from each glucose molecule i.e. 2 ATP per glucose molecule.
• Occurs in mitochondria.	• Occurs in cytoplasm (cytosol).

Evolutionary significance of glycolysis

The role of glycolysis in both fermentation and respiration suggests that ancient prokaryotes probably used glycolysis to make ATP long before oxygen was present in the atmosphere. ***This conclusion is based on the following observations:*** **(1)** The oldest bacterial fossils date back 3.5 billion years, yet oxygen accumulated about 2.7 billion years ago. Therefore early prokaryotes may have generated ATP exclusively from glycolysis, which does not require oxygen. **(2)** Glycolysis is the most widespread metabolic pathway, which suggests that it evolved very early in the history of life. **(3)** Glycolysis is located in the cytoplasm where no membrane-bounded organelles are required in eukaryotic cells, which evolved approximately 1 billion years after the prokaryotic cell.

FATE OF PYRUVATE IN AEROBIC CONDITIONS (TRANSITION STATE OF PYRUVATE)

Each pyruvate molecule produced by glycolysis in the cell cytoplasm is transported across the inner mitochondrial membrane by **active transport** (since it is a charged molecule) into the **matrix**, where it is

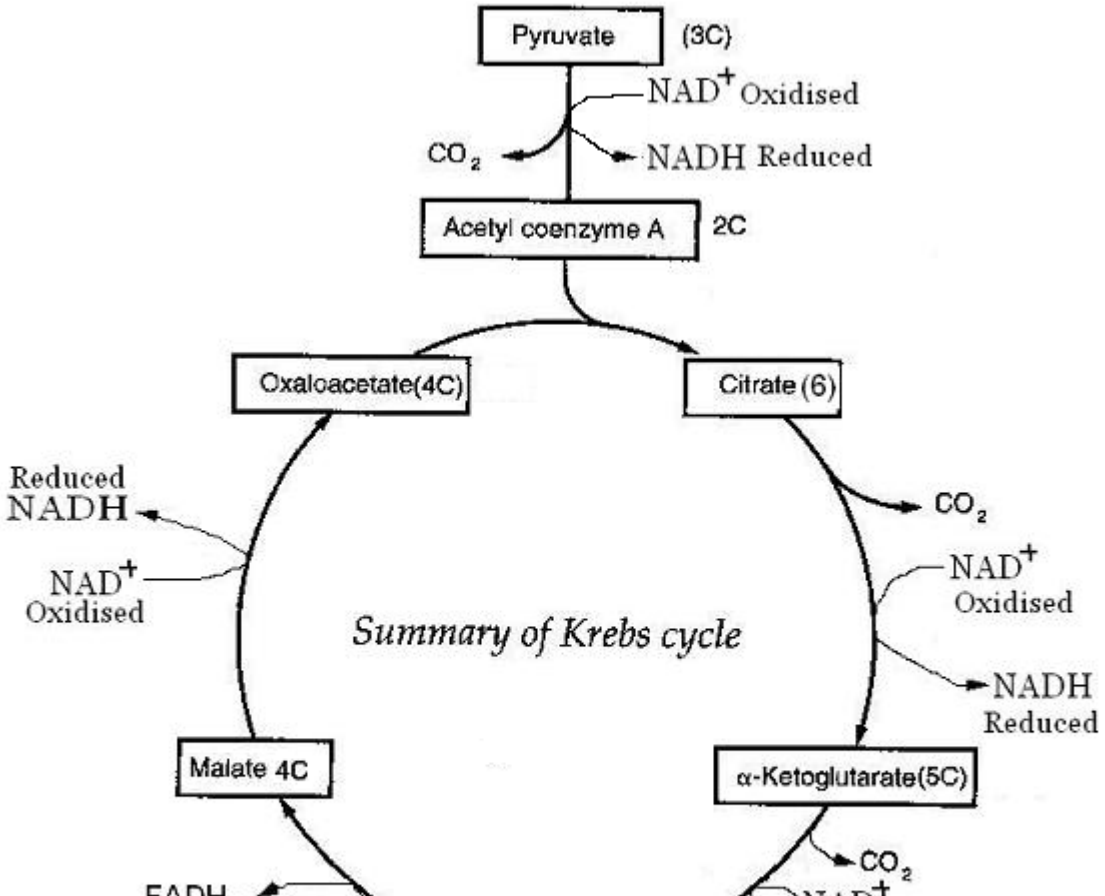
first **decarboxylated** and then **oxidised** (dehydrogenated) to form a 2-C compound called **acetate**, carbondioxide and NADH. Carbondioxide, a waste product is eventually excreted while NAD+ serves as a hydrogen carrier.
Finally, Acetate is attached to Coenzyme A to form acetyl coenzyme A, making the acetyl group very reactive. Acetyl coenzyme A is now ready to feed its acetyl group into the citric acid cycle for further oxidation. (A – stands for acetylation)

Note: *the transition from pyruvate to acetyl coenzyme A is not usually considered as a separate phase and is included with the first step of Krebs cycle.*

THE ROLE OF CoA IN RESPIRATION
(1) Within the active centre of the enzyme **citrate synthetase,** CoA transfers the 2-carbon **acetyl group** to a 4-carbon molecule of **oxalocetate** to make a molecule of **citrate** which enters the Krebs cycle. **(2)** it serves as a link between many different pathways of metabolism to provide a wide range of carbon compounds needed in the cell **(3)** during energy deficiency, amino acids from proteins and fatty acids from lipids can be broken down to provide acetyl CoA for use in respiration.

Acetyl- Coenzyme A: *a central metabolic intermediate*
All proteins, lipids, and carbohydrates must be converted to **Acetyl- Coenzyme A** prior to participation in cellular respiration.
The fate of *acetyl-CoA* is dependent upon ATP needs. When ATP is prevalent, *acetyl-CoA* serves as the basis for fatty acid synthesis, which forms the basis of your body's long-term energy storage: triglycerides (i.e., fat). ***Acetyl-CoA* is the starting point for anabolic pathways that result in the synthesis of fatty acids.** Alternatively, *acetyl-CoA* may enter the Kreb's citric acid cycle.

KREBS CYCLE/ TRICARBOXYLIC ACID CYCLE / CITRIC ACID CYCLE
It is named:
1. Krebs cycle after the formulator Hans Krebs
2. Citric acid because citric acid is the first compound formed.
3. Tricarboxylic acid because citric acid which is the first compound formed has 3 carboxyl (-COOH) groups
It is a multi-step reaction in the mitochondrial matrix during which an acetyl group is completely oxidized to CO_2 with the generation of ATP and reducing hydrogens in the form of NADH and $FADH_2$.



1st Reaction: Prior to entering the Krebs Cycle, pyruvate must be converted into acetyl CoA Acetyl CoA adds its 2-C acetyl group to a 4-C oxaloacetate to form a 6-C citrate molecule.
2nd reaction: citrate isomerizes to a more reactive isocitrate by both removal and addition of one water molecule.
3rd reaction: isocitrate is decarboxylated (loses a carbondioxide) and then oxidized (loses hydrogen to NAD+ to form NADH) to form α-ketoglutarate.
4th reaction: α-ketoglutarate loses a carbondioxide (is decarboxylated) and is oxidised (loses hydrogen to NAD+ to form NADH) and attached to coenzyme A to form succinyl-CoA.
5th step: succinyl-CoA causes phosphorylation of ADP to ATP and the formation of succinate.
6th reaction: a 4-C succinate loses two hydrogens to FAD (is dehydrogenated), forming $FADH_2$ and a 4-C fumarate.
7th reaction: fumarate is hydrated (a water molecule is added) and rearranged to form malate.
8th reaction: finally, malate loses hydrogen to NAD+ to form NADH (is oxidised) regenerating oxaloacetate.

Note:
(1) Carboxylic acids are represented in their ionized forms as $-COO^-$ because the ionized forms prevail at the PH within the mitochondrion. E.g. citrate is the ionized form of citric acid.
(2) The regeneration of oxalocetate makes the process a cycle
(3) For each acetyl group that enters the cycle, 3 NAD+ are reduced to NADH (reactions 3, 4, and 8)
(4) Most of the ATP out put of respiration results from oxidative phosphorylation, when the NADH and FADH2 produced by the citric acid cycle relay the electrons extracted from food to the electron transport chain.

Comparison of Krebs cycle and glycolysis
Similarities: In both: **(1)** reducing hydrogens are accumulated in NADH **(2)** ATP is generated **(3)** there is a reduction in number of carbon atoms of organic compounds**(4)** pyruvate participates **(5)** both occur in living cells

Differences:

Glycolysis	Krebs cycle
• The electron acceptor FAD is **not** involved	• The electron acceptor FAD is involved
• Carbondioxide doesn't form	• Carbondioxide is liberated
• Occurs in cell cytoplasm	• Occurs in mitochondrial matrix
• Doesn't necessarily depend on oxygen	• Depends on oxygen availability to occur

ELECTRON TRANSPORT SYSTEM AND CHEMIOSMOTIC THEORY
Electron transport system: A process whereby a series of electron carriers operate together to transfer electrons from donors to any of several different terminal electron acceptors to generate a transmembrane electrochemical gradient in the mitochondrion

What are the components of the electron transport chain?

Complex	Name	Prosthetic Groups
Complex I	NADH Dehydrogenase	FMN, 9 Iron-Sulphur (Fe-S) centres
Complex II	Succinate-Coenzyme Q Reductase	FAD, cyt b_{560}, 3 Fe-S centers
	Coenzyme Q (CoQ) (also called ubiquinone)	cyt b_H, cyt b_L, cyt c_1, Fe-S
Complex III	Cytochrome bc1 complex	Cytochrome b_1 heme, b_2 heme
Cytochrome c		cyt c
Complex IV	Cytochrome Oxidase	cyt a, cyt a_3, copper (Cu_A)and (Cu_B)

1. NADH dehydrogenase (complex I) **2.** Succinate coenzyme Q reductase (complex II) **3.** Coenzyme Q (CoQ) (also called ubiquinone) **4.** Cytochrome bc1 complex (complex III) **5.** Cytochrome c (Cyt c) **6.** Cytochrome oxidase (complex IV)

Cytochromes: are proteins with **heme** prosthetic groups. **Heme** contains an iron atom embedded in a porphyrin ring system. They absorb light at characteristic wavelengths.
Iron-sulfur centers (Fe-S): are prosthetic groups containing **2, 3, 4, or 8 iron atoms**, complexed to a combination of elemental and cysteine **sulfur atoms**.
NAD^+ (Nicotinamide Adenine Dinucleotide): is a coenzyme containing the B-vitamin, **niacin**. NAD^+ accepts 2 e^- and one H^+ (a hydride) in going to the reduced state, as **$NAD^+ + 2\ e^- + H^+$ « NADH.** It may also be written as: **$NAD^+ + 2\ e^- + 2H^+$ « NADH + H^+**
NAD^+ is a **coenzyme**, that reversibly binds to enzymes.

FAD (Flavin Adenine Dinucleotide): is derived from the vitamin riboflavin (B2). The protein to which it is attached is termed a **flavoprotein (FP).** FAD normally accepts 2 e^- and 2 H^+ in going to its reduced state:
$FAD + 2\ e^- + 2\ H^+$ « $FADH_2$
FAD is an electron-carrier coenzyme like NAD+. However, unlike NAD+, FAD always occurs as a **prosthetic group**, tightly bound at the active site of an enzyme, never as a free carrier.

FMN (Flavin MonoNucleotide): is a prosthetic group of some flavoproteins. It is similar in structure to FAD, but lacking the adenine nucleotide.

LOCATION OF THE CONSTITUENTS OF THE ELECTRON TRANSPORT CHAIN
Most constituents of the respiratory chain are embedded in the inner mitochondrial membrane. **Coenzyme Q (Ubiquinone):** is located within the lipid core of the inner membrane. As its name suggests, is very widely distributed in nature. CoQ acts as a bridge between enzyme complex 1 and 3 or between complex 2 and 3.**Cytochrome c** resides in the intermembrane space (within the lumen of the cristae). It alternately binds to Complex III or Complex IV during electron transfer.

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FAD $FADH_2$

The production of ATP during elec
Chemiosmosis and oxidative phos

Description of the process of
The electrons released during glycolysis and carried by NADH are converted to $FADH_2$ in order to shuttle them from the cytoplasm into the mitochondrial matrix.

In Complex I (also called NADH reductase), reduced nicotinamide adenine dinucleotide **(**NADH) donates electrons to the coenzyme Flavin mononucleotide (FMN) which then passes electrons to an iron-sulphur (Fe-S) protein and the electrons lose some energy. **NADH** is oxidized to **NAD^+,** while **FMN and Fe^{3+}** are **reduced**

to $FMNH_2$ and Fe^{2+} respectively. Each electron is transferred with a proton.
Electrons from the reduced Fe-S proteins are then passed to Coenzyme Q along with protons. Coenzyme Q is thus reduced while the Fe-S proteins are oxidised back to Fe^{3+} state.

In **complex II (succinate dehydrogenase),** electrons from $FADH_2$ are passed on to Fe-S proteins then to Coenzyme Q which transfers them to **complex III**. **$FADH_2$** becomes oxidised to **FAD+.** During this process, four protons (H^+) are translocated across the inner mitochondrial membrane, from the matrix to the intermembrane space. This creates a proton gradient that will be later used to generate ATP through oxidative phosphorylation. During oxidation of $FADH_2$ complex I is bypassed because complex II has only enough reducing potential to pass electrons to Coenzyme Q.

Reduced coenzyme Q ($CoQH_2$) transfers electrons to **Complex III** where they pass through several cytochromes and Fe-S proteins and during the process Fe^{3+} is reduced to Fe^{2+}. The electrons lose additional energy and are passed on to cytochrome *c* which passes electrons to **Complex IV (cytochrome *c* oxidase**), which finally transfers the electrons to reduce molecular oxygen to form **water.** $O_2 + 4\ H^+ + 4\ e^{-} \rightarrow 2\ H_2O$. At the same time, complex IV moves protons (H+) across the membrane into the intermembrane space, producing a proton gradient.

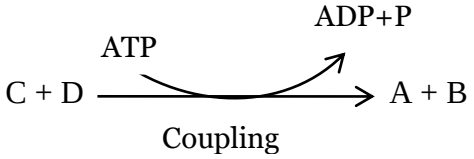
As electrons lose energy in complex I, III and IV, additional protons are pumped into the intermembrane space producing a proton gradient. **Complex II (succinate dehydrogenase)** is not a proton pump. It only serves to funnel additional electrons into coenzyme Q. Electron transfers involving Coenzyme Q and Cytochrome c do not release enough free energy to pump any protons.
When the protons flow down the concentration gradient through the channels in the stalked particles, ATP synthase enzymes are able to use the energy to generate ATP.

Note: If the oxygen supply is cut off, the electrons and hydrogen protons cease to flow through the electron transport system. If this happens, the proton concentration gradient will not be sufficient to power the synthesis of ATP. This is why we, and other species, are not able to survive for long without oxygen!

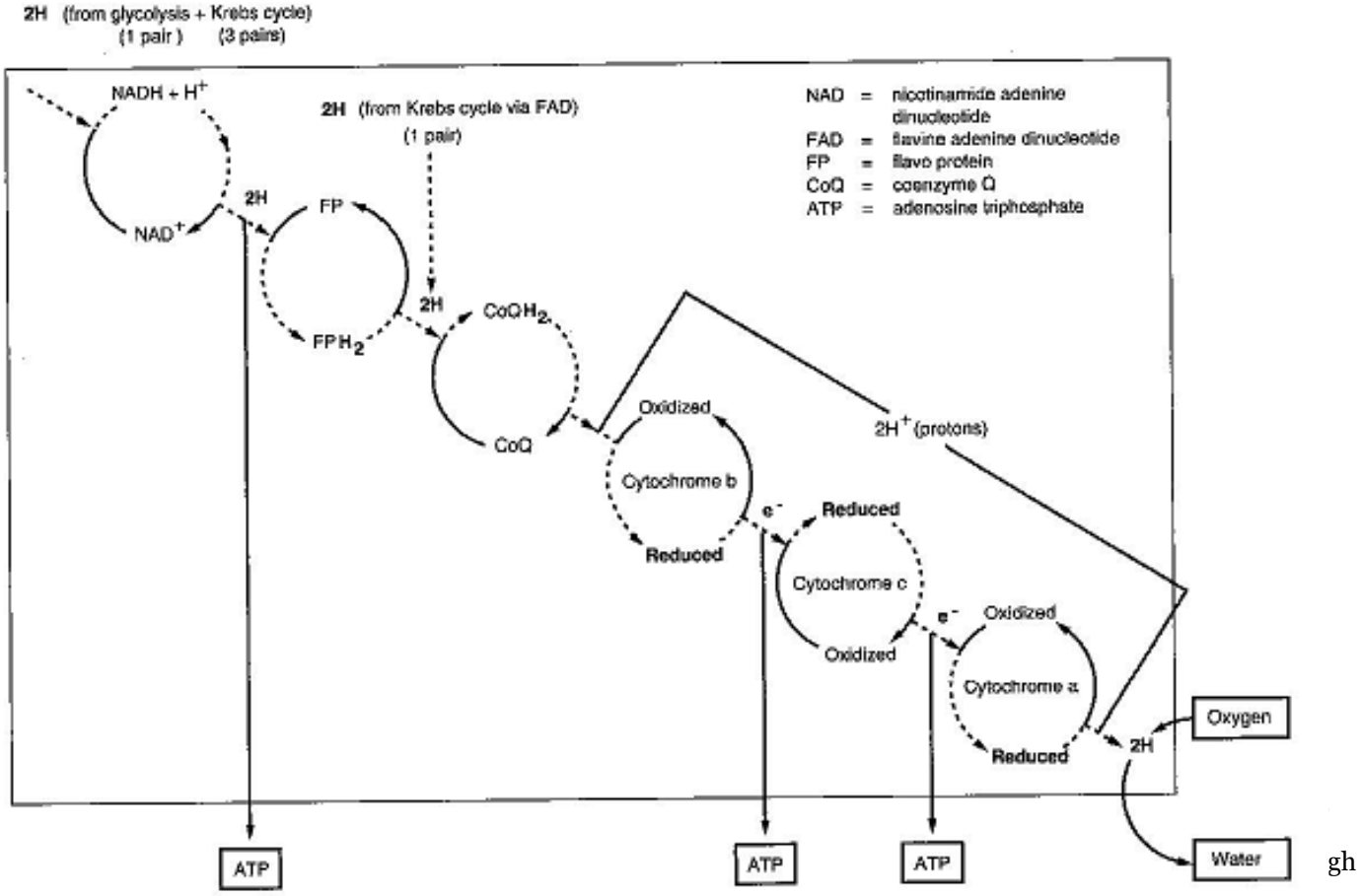
Is the ETS a sequence?
No! The complexes move in the fluid membrane independently of one another, and exchange electrons when they are in mutual proximity. Although textbooks show the ETS as a physical sequence, the complexes and carriers are not locked in place.

CHEMIOSMOTIC COUPLING HYPOTHESIS AND OXIDATIVE PHOSPHORYLATION
As proposed by Peter D. Mitchell, the chemiosmotic coupling hypothesis explains that the electron transport chain and oxidative phosphorylation are coupled by a proton gradient across the inner mitochondrial membrane.
The efflux of protons into the intermembrane space creates both a **pH gradient** and an **electrochemical gradient**. This proton gradient is used by the ATP synthase complex to make ATP via **oxidative phosphorylation**. The stalk component of ATP synthase complex acts as an ion channel for return of protons back to mitochondrial matrix during which the free energy produced during the generation of the oxidized forms of the electron carriers (NAD^+) is released and used to drive ATP synthesis, catalyzed by the head component of the ATP synthase complex.

Definition of coupled reactions:
Reactions that occur in the same place, at the same time and in such a way that an energy releasing-reaction can drive an energy requiring-reaction. Usually, the energy releasing reaction is ATP breakdown. Below is a simplest representation of a coupled reaction.



Summary of the electron (hydrogen) transport system



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In some text books however, recent information suggests that 1NADH generates 2.5 ATP and 1FADH$_2$ generates 1.5 ATP. The reasons for this are that not all of the energy stored in the proton gradient is used to generate ATP. Some of the energy is used to power transport of ions in and out of the mitochondria.

A total of 12 pairs of electrons and hydrogens are transported to the electron transport system from glycolysis and Krebs cycle for each glucose molecule that enters the process:

- 4 pairs are carried by NADH and were generated during glycolysis in the cytoplasm, 8 pairs are carried as NADH and were generated within the mitochondrial matrix and 2 pairs are carried by $FADH_2$ and were generated within the mitochondrial matrix.
- For each of the 8 NADHs generated within the mitochondrial matrix, enough energy is released to produce 3 ATP molecules; therefore, 24 ATP molecules are released from these electrons carried by NADH.
- The electrons carried by FADH2 are lower in energy, so during the oxidation-reduction reactions, they release energy to produce only 8 ATP molecules.
- Therefore, a grand total of 32 ATP molecules are produced from hydrogen electrons that enter the electron transport system.

WHAT QUANTITY OF ATP IS GENERATED BY CHEMIOSMOSIS FROM ONE MOLECULE OF GLUCOSE DURING THE ELECTRON TRANSPORT CHAIN?

The chemiosmotic model suggests that one ATP molecule is generated for each H^+ pump activated by the electron transport chain. Since the electrons from NADH activate **three pumps** and those from $FADH_2$ activate **two**, it would be expected that the numbers of ATP molecules generated by each molecule of NADH and $FADH_2$ are t**hree** and **two** respectively. However, since the transportation of the **two** molecules of NADH produced during Glycolysis into the mitochondrion requires **two ATPs**, the theoretical yield from aerobic respiration = 36 molecules of ATP i.e. 4 (from substrate-level Phosphorylation) + 30 (3 from each of 10 molecules of NADH) + 4 (2 from each of 2 molecules of $FADH_2$) – 2 (for transport of glycolytic NADH). The

actual yield is less than 36 because **(1)** the inner mitochondrial membrane allows some H^+ to re-enter the matrix without passing though ATP-generating channels **(2)** mitochondria often use the proton gradient generated by chemiosmosis for purposes other than ATP synthesis e.g. transporting Pyruvate into the matrix. As a result, the measured values of ATP generated are closer to 2.5 for each NADH and 1.5 for each $FADH_2$. The molecules of ATPs formed from one molecule of glucose = 30 i.e. 4 (from substrate-level Phosphorylation) + 25 (2.5 from each of 10 molecules of NADH) + 3 (2 from each of 2 molecules of $FADH_2$) – 2 (for transport of glycolytic NADH)

SUMMARY OF THE RESPIRATORY STAGES OF ONE GLUCOSE MOLECULE

Process	Where it occurs	Number of Molecules of Reactants	Number of Molecules of Products	Molecules of ATP gained	
				Theoretical	Net/ Actual
Glycolysis	**Cytoplasm** (most organisms) **Glycosomes*** (trypanosomes)	1 Glucose 2 ATP 4 ADP + 4 P_i 2 NAD^+ + 2 H^+	2 Pyruvate 2 ADP + 2 P_i 4 ATP 2 NADH 2 H_2O	04**	02
Krebs cycle/ Tricarboxylic acid cycle / citric acid cycle	Mitochondrial matrix	2 Pyruvate 2 ADP + 2 P_i 8 NAD^+ + 8 H^+ 2FAD + 4 H	6 CO_2 2 ATP 8 NADH 2 $FADH_2$	02	02
Electron transfer system **&** chemiosmosis (oxidative Phosphorylation)	Inner mitochondrial membrane	8NADH+24ADP+24 P_i 2$FADH_2$+8ADP+8P_i 6 O_2 + 24 H^+	8NAD^++24ATP+16 H 4FAD+8ATP+8H 12 H_2O	**34**	**30**

Glycosomes*: Are organized cytoplasmic organelles in trypanosomes, the parasitic protozoans that cause African sleeping sickness

04:** Because two molecules of ATP are used to start the process and a total of four ATPs are generated, each glucose molecule that undergoes Glycolysis produces a net yield of two ATPs.

The purpose of the several steps in the electron transport chain:
1) to pass along $2H^+$ ions and $2e^-$ to eventually react with oxygen;
2) to conserve energy by forming three ATP's; and
3) to regenerate the coenzymes back to their original form as oxidizing agents.

Inhibitors of electron transport

Inhibitors	Action
Cyanide and Carbon monoxide	Block cytochrome oxidase enzyme in complex IV
Rotenone	Blocks complex I. It's a common rat poison
Antimycin	Blocks electron transfer in complex III
Oligomycin	Blocks the proton channel in ATP synthase

Inhibitors bind to the components of the electron transport chain and block electron transfer. All components before the block are stuck in a reduced state and all components after in an oxidised state. No electron transfer is possible and proton pumping stops. The proton gradient is quickly run down and ATP synthesis stops. Inhibitors may also block the proton channel of ATP synthase.

EFFICIENCY OF RESPIRATION

Not all the energy present in the high-energy hydrogen atoms is conserved as ATP. Part of the energy is released as heat used for the maintenance of body temperature, but if it is in excess then it can be dissipated to the external environment.
The efficiency of energy conserved in aerobic respiration, alcoholic fermentation and lactic acid fermentation are thus as follows:

Aerobic respiration	Alcoholic fermentation	Lactic acid fermentation
A total of 38 molecules of ATP are formed while the amount of energy released is 2880KJ. To form 1 molecule of ATP requires 30.6kj. Thus the amount of energy used to form 38 molecules of ATP is equal to 38 x 30.6 = 1162.8KJ.	Alcohol fermentation releases 210KJ with the formation of 2ATP. To form 1 molecule of ATP requires 30.6kj. Thus the amount of energy used to form 2 molecules of ATP is equal to 2 x 30.6 = 61.2KJ.	Lactic acid fermentation releases 150KJ with the formation of 2ATP. To form 1 molecule of ATP requires 30.6kj. Thus the amount of energy used to form 2 molecules of ATP is equal to 2 x 30.6 = 61.2KJ.
Efficiency of energy conserved= $\frac{38ATP \times 30.6KJ}{2880} \times 100$ = 40.375 ≈ 40.4%	*Efficiency of energy conserved =* $\frac{2ATP \times 30.6KJ}{210} \times 100$ = 29.1%	*Efficiency of energy conserved =* $\frac{2ATP \times 30.6KJ}{150} \times 100$ = 40.8%
The remaining 1717.2KJ(59.6%) is released as heat	The remaining 148.8KJ(70.9%) is released as heat	The remaining 88.8KJ(59.2%) is released as heat
However, considering that glucose on complete oxidation releases 2880KJ of energy, the yield from anaerobic respiration is given by: $\frac{2ATP \times 30.6KJ}{2880} \times 100 = 2.1\%$ Therefore, on a whole anaerobic respiration is 2% efficient.		

ENERGY FROM LIPIDS, PROTEINS AND HEXOSES OTHER THAN GLUCOSE (e.g. FRUCTOSE ,GALACTOSE AND MANNOSE)

Energy from lipids (fat and oil):

In the gut, the enzyme lipase catalyses the hydrolysis of lipids into fatty acids and glycerol which enter the lacteal and finally gain entry into liver cells.

Glycerol is phosphorylated with ATP, dehydrogenated with NAD and converted to triose phosphate (glyceldehyde-3-phosphate) which is fed into the glycolysis pathway. There is a net yield of **19 molecules of ATP** from the oxidation of triose phosphate and of the NADH formed.

The fatty acid component is progressively broken in the matrix of the mitochondria into fragments of 2 carbons each which are converted to acetyl coenzyme A. This then enters the Krebs cycle with subsequent release of energy.

Carbohydrates versus Fats in energy release

Aspect	Explanation
Amount of energy released	Gram for gram, fats provide more energy than carbohydrates. The reason for this is the amount of oxidation that takes place as these compounds are converted to carbon dioxide and water. Carbon for carbon, fats require more oxidation to become CO_2 and H_2O than do carbohydrates. Roughly, carbohydrates already have one oxygen for every carbon atom, thus each carbon atom needs only one more oxygen and each pair of hydrogen atoms needs one more oxygen. However, almost every carbon atom in a fat molecule needs two oxygens instead of just one additional one, and each pair of hydrogen atoms still needs one more oxygen. So, just from counting the number of oxygens needed to be added, fats require about half again as much oxygen for the same number of carbon atoms. Because of this, the oxidation of fats takes longer, but it also gives off more energy. When comparing gram to gram, instead of carbon to carbon, the effect is exaggerated. When you weigh a carbohydrate, more oxygen is included in that weight. When you weigh a fat, you get more carbon atoms per gram and therefore, gram for gram, the fats will give even more energy (over twice as much) than will the carbohydrates.

Time spent	**Carbohydrates** enter into the oxidation process much more quickly and **provide energy more rapidly than fats.** This is because **fats** go through several more steps than do carbohydrates to become acetyl CoA and enter the citric acid cycle.

ENERGY FROM PROTEIN

The body resorts to protein as an energy source only during starvation.
Catalysed by the enzymes, protein is first hydrolysed to amino acids which are then individually deaminated i.e. amino groups (-NH2) are removed and converted to ammonia, urea or uric acid for excretion. The residual carbon compound (a keto acid) then enters the respiratory pathway at a number of points depending on their number of carbon atoms. E.g. 5-carbon amino acids like glutamate are converted to α-ketoglutarate, 4-carbon amino acid like aspartate are converted to oxaloacetate. Both α-ketoglutarate and oxaloacetate are Krebs cycle intermediates. 3-carbon amino acids like alanine are first converted to pyruvate and then acetyl coenzyme A. other amino acids with larger number of carbon atoms are converted by transamination reactions into 3, 4 or 5-carbon amino acids.

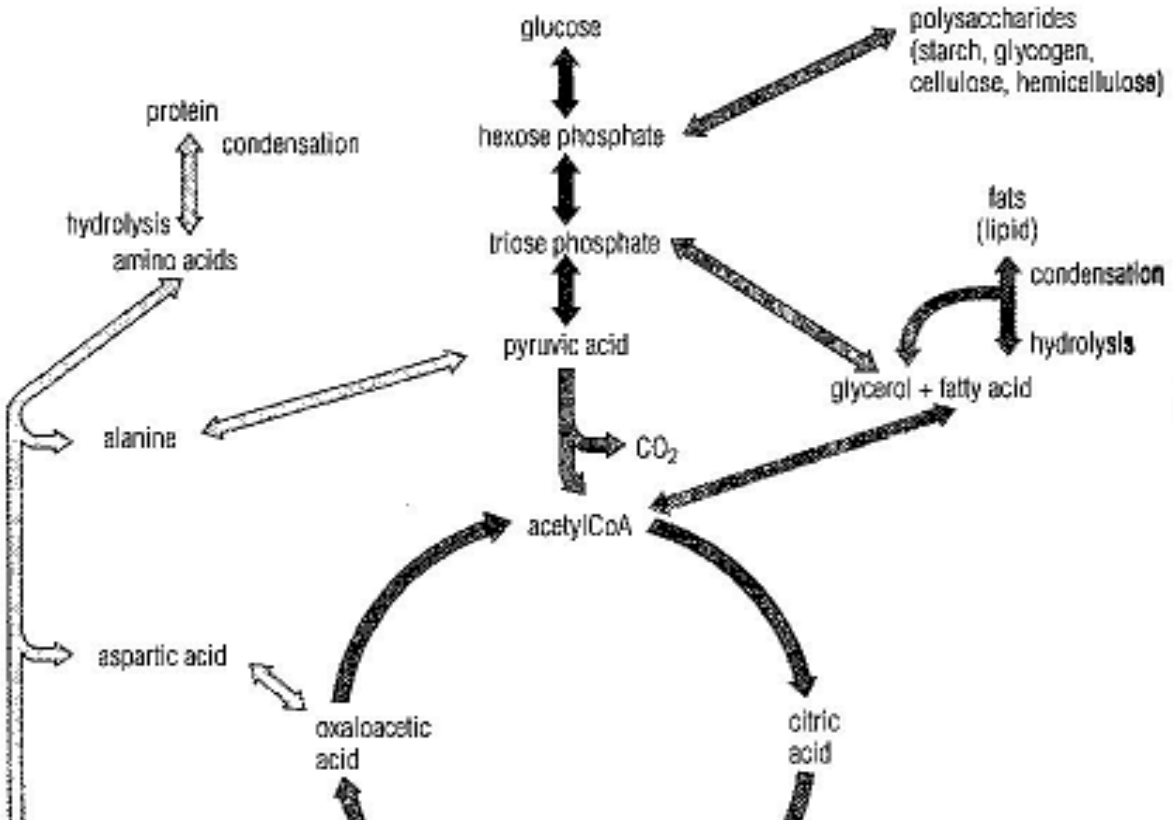
OTHER MONOSACCHARIDES ENTER THE GLYCOLYTIC PATHWAY AT SEVERAL POINTS

In most organisms, hexoses other than glucose can undergo glycolysis after conversion to a phosphorylated derivative.

1. FRUCTOSE: is present in free form in many fruits and is also formed by hydrolysis of sucrose in the ileum of vertebrates. In the muscles and kidney fructose is phosphorylated to fructose-6-phosphate by hexokinase enzyme while in the liver fructokinase enzyme catalyses the phosphorylation of fructose to fructose-1-phosphate which then splits into glyceraldehyde and dihydroxyacetone phosphate.
Dihydroxyacetone phosphate converts to glyceraldehyde 3-phosphate while glyceraldehyde is phosphorylated by ATP to glyceraldehyde 3-phosphate. Thus both products of fructose 1-phosphate hydrolysis enter the glycolytic pathway as glyceraldehyde 3-phosphate.

2. GALACTOSE: is a product of hydrolysis of the disaccharide lactose (milk sugar). Galactose is first phosphorylated by ATP to galactose-1-phosphate and then converted to glucose-1-phosphate through a series of reactions.
Galactosemia is a human genetic disease that results from disordered galactose metabolism in which the overall conversion of galactose to glucose prevented.
MANNOSE, which is released in the digestion of various polysaccharides and glycoproteins of foods, can be phosphorylated at C-6 by hexokinase:
Mannose + ATP → mannose 6-phosphate + ADP
Mannose 6-phosphate then isomerizes to fructose 6-phosphate, an intermediate of glycolysis.

Tissue respiration and its connections with the rest of metabolism



CONTROL OF RESPIRATION
Because the principle function of respiration is to produce ATP, it must be regulated so that ATP is generated only when needed. This occurs in a number of ways:
1. At cellular level, the rate at which respiration occurs is regulated mainly by the energy state of the cell (i.e. the ratio of ATP to ADP), acting via regulatory enzymes. High levels of ATP (high energy level of the cell) inhibit the enzyme **hexokinase** that catalyses phosphorylation of glucose at the start of glycolysis while low energy levels (high ADP levels) stimulate **hexokinase** enzyme. Highly active cells utilize ATP very fast breaking it to ADP. This has the effect of enhancing the rate of respiration. Such cells include **liver cells, striated muscle cells, spermatozoa** and **nerve cells**. They are characterized by presence of numerous mitochondria. Less active cells utilize ATP slowly and hence respiration in them is slow e.g. **fat cells**.
2. At the level of the whole organism, the respiratory rate is influenced by **environmental factors** e.g. temperature, **structural factors** e.g. body size and **physiological factors** such as level of activity, growth and dormancy.

Temperature: generally, very low temperature slows down respiration in both homoiotherms and poikilotherms, although it can be observed that homoiotherms need increased respiration rate to generate much heat for maintaining body temperature. In poikilotherms temperature near to that of the body increases the respiration rate. *This partly explains why mosquitoes and tsetse flies are only found in the tropics where environmental temperature is close to their optimal temperature.* High temperature slows down the respiration rate in homoiotherms. This explains why such animals tend to be sluggish during hot weather. However, excessively high temperatures trigger increased respiration rate and finally stop as a response by enzymes to temperature.

Body size: small organisms with a large surface area to volume ratio lose heat faster and therefore respire faster than large organisms.
Level of activity: animals engaging in vigorous physical exercise require much energy and so experience faster respiration rate e.g. sprinting, flying, etc
Growth: actively growing organisms e.g. young animals and germinating seeds respire faster to generate much energy required to drive metabolic processes
Dormancy during extreme cold and hot seasons: respiration rate is always slow to avoid depleting food reserves before the unfavourable season ends.

RESPIRATORY QUOTIENT (RQ)
It is the ratio of the volume of Carbondioxide produced to the volume of oxygen used in respiration during the same period of time

$$RQ = \frac{\text{volume of Carbondioxide given out}}{\text{Volume of oxygen taken in}}$$

Importance of RQ:
(1) it can indicate the kind of substrate being respired (2) it can indicate whether the respiration is aerobic or anaerobic.
RQ can be measured using a **spirometer** or **respirometer.**

RQ FOR HEXOSE SUGAR: like glucose, the equation for its complete oxidation is:

$C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$

Hence RQ is: $\frac{6CO_2}{6O_2} = 1.0$ (one)

R.Q FOR FATS: For a lipid like tripalmitin, the equation for its complete oxidation is:

$$2\,(C_{51}H_{98}O_6) + 145\,O_2 \longrightarrow 102\,CO_2 + 98H_2O + \text{energy}$$

Tripalmitin

RQ is: $\frac{102CO_2}{145O_2} = 0.7$ (less than one)

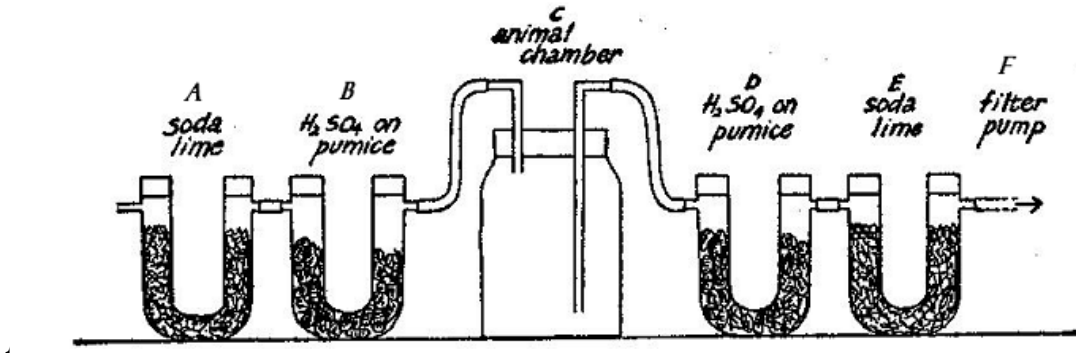
NB: the R.Qs for different fats will of course show slight variations because of differences in molecular composition

R.Q FOR PROTEINS: no concrete value can be calculated since **(1)** they vary so much in composition and **(2)** are difficult to separate in the pure state. Estimates for protein vary between 0.5 and 0.8 for the complete oxidation of proteins.

SUMMARY OF THE POSSIBLE INTERPRETATIONS OF R.Q VALUES:

Subject	R.Q.	Possible interpretations
Germinating starchy seeds aves rich in carbohydrate	1.0 1.0	Complete oxidation of a carbohydrate substrate
Wheat seedlings in nitrogen	∞	Anaerobic respiration
Germinating linseeds	0.64	Oxidation of a fatty substance
Germinating peas	3.0 to 4.0	Slow entry oxygen causing some anaerobic respiration
Germinating peas (testa removed)	1.5 to 2.5	More rapid entry of oxygen, but some anaerobic respiration
Man (average)	0.8 to 0.85	Mixed fat and carbohydrates substrate
Lumbricus terrestris	0.75	Mainly fat substrate
Drosophila (at rest)	1.23	Conversion some carbohydrate to fat : excess CO_2 produce by decarboxylation
Drosophila (flying)	1.0	Complete oxidation carbohydrate
Nerve tissue (resting)	0.77	Possibly mainly fat substrate
Nerve tissue (active)	0.97	Almost entirely carbohydrate substrate

Measurement of R.Q. for small animals e.g. frog or a few earthworms



hen the apparatus is connected, C is placed in a vessel of cold water to keep its temperature constant, and the pump is run for 10 to 20 minutes. After the experiment, the weight of Carbondioxide exhaled is the gain in the weight of E. the weight of water given off by the animal is the gain in weight of D. the weight of substrate used is the loss in weight of the animal. Hence, the weight of oxygen absorbed can be obtained thus:

Substrate + oxygen = Carbondioxide + water.
Oxygen used = (Carbondioxide + water) – substrate
= (gain in weight of E + gain in weight of D) – loss in weight of animal

The weights of Carbondioxide and oxygen thus obtained can be converted into volumes, and thus the R.Q. obtained.

Precautions to be considered: **(1)** the soda-lime and sulphuric acid containers should be doubled in each case **(2)** the animal container C must be carefully dried after the experiment and before weighing **(3)** all vessels must not be touched by the hand but by strong wooden forceps.

COMPARISON OF RESPIRATION WITH PHOTOSYNTHESIS

Differences:	**Photosynthesis**	**Respiration**
Where they occur	In chlorophyll-bearing cells	In all cells
When they occur	In the presence of light	All the time
Input	Carbon dioxide and water	Reduced carbon compounds and oxygen
Output	Reduced carbon compounds, oxygen, and water	Carbon dioxide and water
Energy sources	Light	Chemical bonds
Energy result	Energy stored	Energy released
Chemical reaction	Reduction of carbon compounds	Oxidation of carbon compounds
Energy carrier(s)	NADP	NAD and FAD

Similarities
Both **(1)** involve converting energy from one form to another **(2)** occur in living cells **(3)** involve the formation of ATP **(4)** require energy to occur **(5)** involve a series of multi-enzyme catalysed reactions **(6)** involve flow of electrons along carriers.

ECONOMIC IMPORTANCE OF ANAEROBIC RESPIRATION
(1) Fermentation is applied in the manufacture of alcoholic drinks like wine making, beer making and manufacture of spirits. **(2)** Fermentation of yeast is used in leavening of bread i.e. production of raised bread **(3)** it is applied in the manufacture of milk products like sour milk, yoghurt and cheese **(4)** is applied in the manufacture of organic acids e.g. citric acid, oxalic acid and butyric acid all of which have several industrial applications especially in food processing.

ATP PRODUCTION DURING EXERCISE
On average, a muscle contains only enough ATP to sustain about 15 seconds of intense exercise. For muscle contractions to continue, massive amounts of ATP are required. Depending on the level of and duration of activity, the muscles being exercised may produce the ATP they need by cellular respiration or by fermentation. Sustained periods of sub maximal activity like jogging are powered by aerobic respiration, but in contrast short periods of intense activity like sprinting are powered by a combination of aerobic and anaerobic respiration.
"Anaerobic" here means a combination of glycolysis and stored ATP/Phosphocreatine release.

The table below shows the relative contributions of anaerobic and aerobic respiration to exercise during a work out.

Duration of maximal exercise										
	Seconds				**Minutes**					
	10	30	60		2	4	10	30	60	120
Percent anaerobic	90	80	70	Percent anaerobic	50	35	15	5	2	1
Percent aerobic	10	20	30	Percent aerobic	50	65	85	95	98	99

[Quoted by Krogh David (2002): Biology; a guide to the natural world (2nd ed.), Prentice Hall; New Jersey, adapted from Astrand, P. O., and Rodahl, K. (1977): textbook of work physiology; McGraw Hill, New York]

Observations:
(1) In the first minute, the energy supply from aerobic respiration is low but rapidly increases while that of anaerobic respiration is high but rapidly decreases.

(2) In the second minute there is equal contribution to energy needs from both aerobic and anaerobic respiration, followed by a rapid increase from aerobic respiration up to the 30th minute and a gradual increase thereafter, while anaerobic respiration decreases rapidly up to the 30th minute and gradually thereafter.

Explanation:

(1) During the first minute, the small amounts of ATP and phosphocreatine stored in cells provide instant energy. When glycolysis starts, it provides a proportionally smaller contribution, and a smaller contribution yet comes from aerobic metabolism. These differences reflect the time it takes for each of these systems to get going.

(2) As the duration of the exercise increases to the ATP/PCr reservoir reduce greatly while the aerobic respiration now predominates.

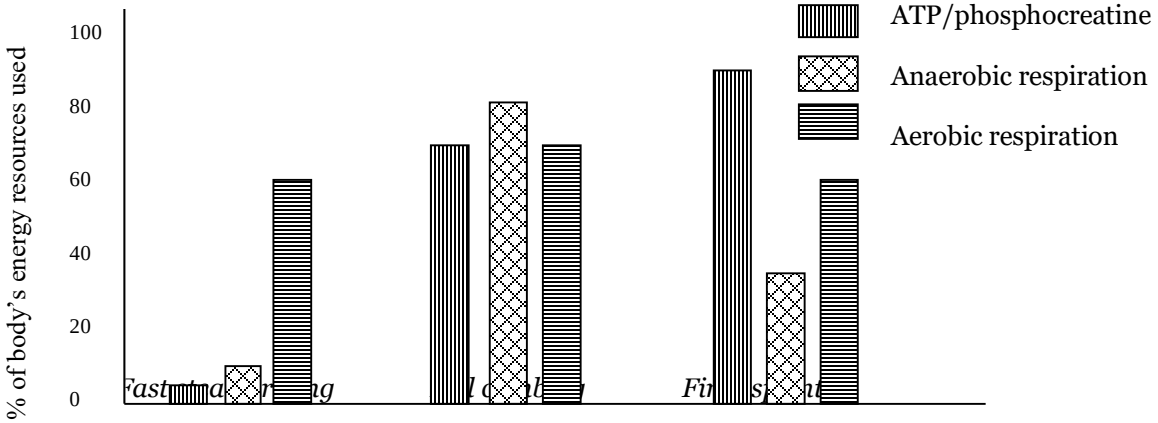
NOTE:

Phosphocreatine (also called creatine phosphate), **stores ~P bonds in** nerve and muscle cells.

Creatine Kinase catalyzes: **phosphocreatine + ADP ⇔ ATP + creatine**

This is a reversible reaction, though the equilibrium constant slightly favors phosphocreatine formation. Phosphocreatine is produced when ATP levels are high. When ATP is depleted during exercise in muscle, phosphate is transferred from phosphocreatine to ADP, to replenish ATP.

The figure below shows how the different energy sources are used at different stages in a bicycle race.



[Quoted by Krogh David (2002): Biology; a guide to the natural world (2nd ed.), Prentice Hall; New Jersey, adapted from Kearney, J. T. (June 1996, p.54): Training the Olympic Athletes, scientific American]

Observations:

(1) During the fast steady riding, there is an overriding contribution of aerobic respiration, but very little from ATP/phosphocreatine and anaerobic respiration.

(2) In the stretches of hill climbing, glycolysis predominates over ATP/phosphocreatine and aerobic respiration in providing energy. The latter two make equal contribution, which follows closely.

(3) In the final sprint, ATP/phosphocreatine takes the leading role in providing energy, followed by aerobic respiration and leastly by anaerobic respiration. This is because during the steady riding, ATP/phosphocreatine reservoirs replenished and therefore provides energy fast to the cells.