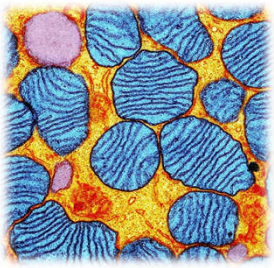
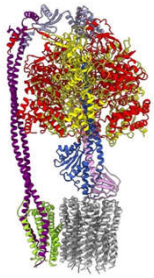
COLUMBIA UNIVERSITY
MEDICAL CENTER

Energy versus death – the problem of mitochondria

Why do we eat? Why do we breathe?
How do we age?

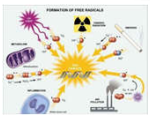




Alexander Galkin

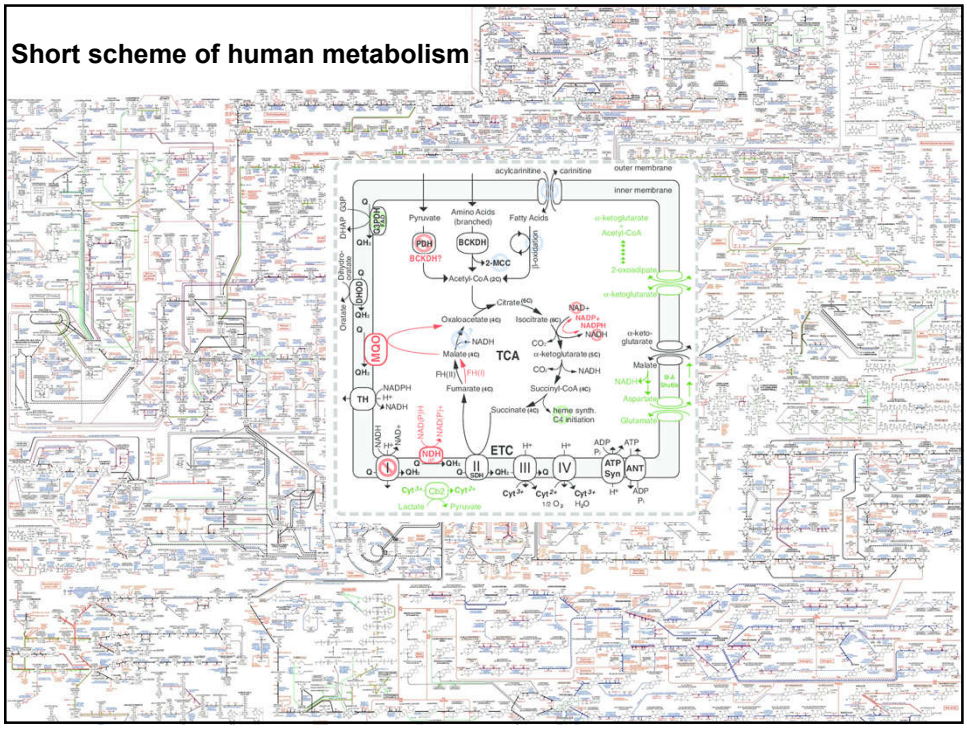
We will talk about

1. General metabolism: catabolism
2. Mitochondria and energy generation
3. Free radicals or ROS
4. Ageing
5. Diet

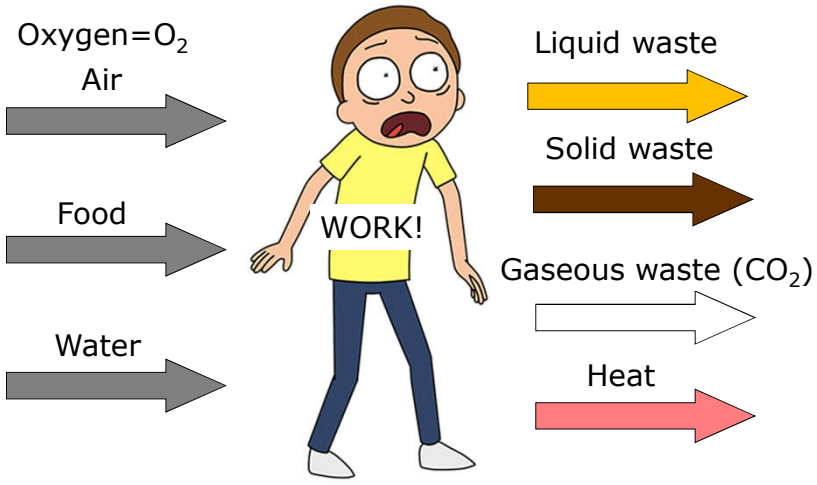




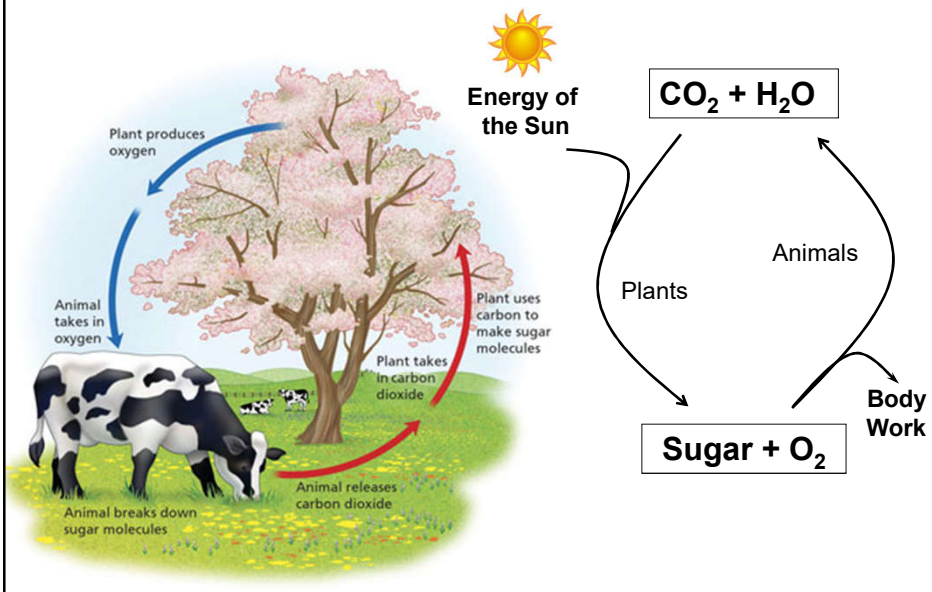
Short scheme of human metabolism



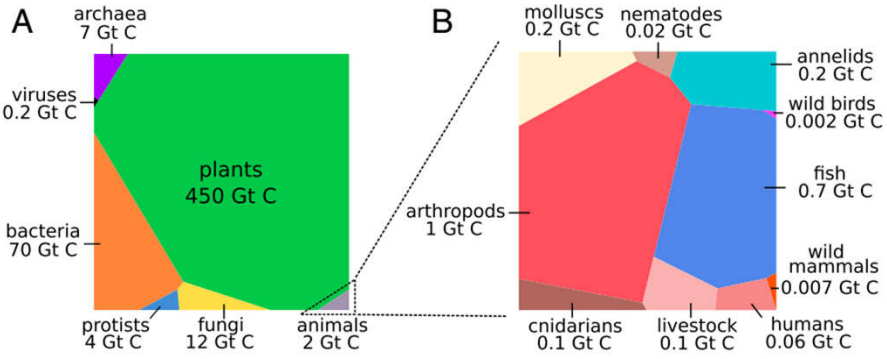
What is coming in and coming out?



Energy and oxygen



The biomass distribution on Earth



Baron et al., 2018, PNAS

What is happening with oxygen?

$$O_2 + 4e^- + 4H^+ \underset{\text{Plants}}{\overset{\text{Animals}}{\rightleftharpoons}} 2H_2O$$

Oxygen molecules are being reduced by our body into water (O_2 accepts electrons=reduction)

RESPIRATION

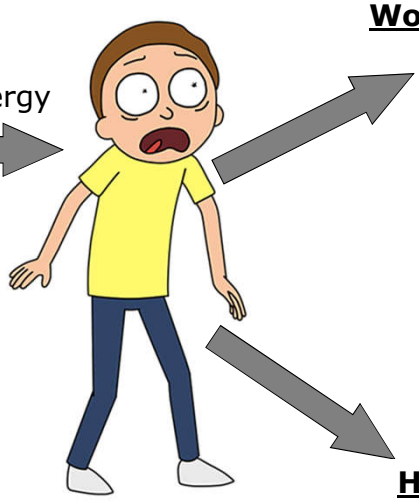
Plants are able to oxidise water molecules and release O_2 (H_2O loses electrons=oxidation)

PHOTOSYNTHESIS

Human body as energy converting machine?

Food = energy

Work = moving, thinking, making new parts, removing wastes



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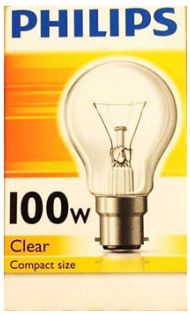


Heat

Very similar to burning, but slower and in a controlled way

How do we measure energy in food?

Nutrition Facts
Serving Size 1 oz. (28g/About 15 chips)

Amount Per Serving	
Calories 160	Calories from Fat 90
	% Daily Value*
Total Fat 10g	**16%**
Saturated Fat 1g	**5%**
Trans Fat 0g	
Polyunsaturated Fat 2.5g	
Monounsaturated Fat 5g	
Cholesterol 0mg	**0%**
Sodium 170mg	**7%**
Potassium 350mg	**10%**
Total Carbohydrate 15g	**5%**
Dietary Fiber 1g	**5%**
Sugars less than 1g	
Protein 2g	
Vitamin A 0% •	Vitamin C 10%
Calcium 0% •	Iron 2%

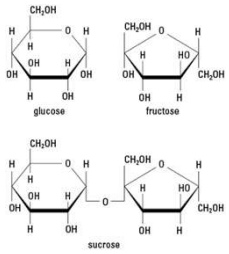
$\Delta H = C \times \Delta T$

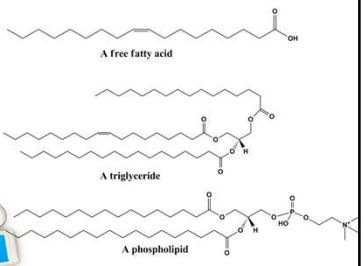
~~No such thing as a negative calorie food~~

Calorimeter

What do we eat?

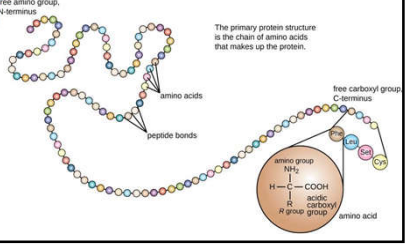
Carbohydrates = Carbs, Sugars, Starch





Fats, lipids

Proteins=polypeptides



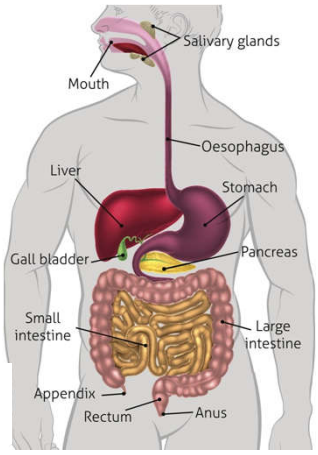
Where does everything go?

Digestive system:

Foodstaff = sugars + proteins + fats

Cook (external digestion!!)
Chewing/wetting
Swallow
Degrade to smaller molecules
- Proteins → amino acids
- Fats → fatty acids and other
- Starch and sugars → glucose

Absorption into blood and go to LIVER!
Controlling point => poison removal



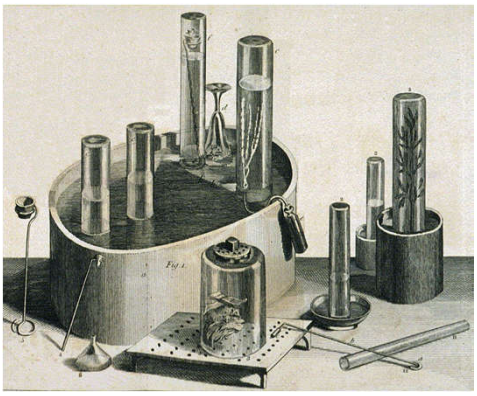
What about air?

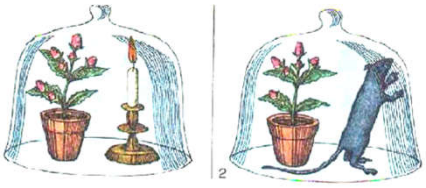
Oxygen!
Air

Food

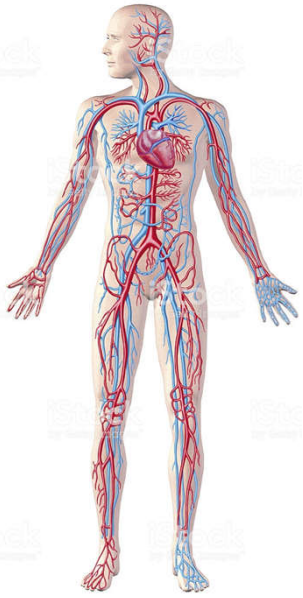
Joseph Priestley
1774-1779

He found that a mouse kept with a plant would survive and candle continues to burn.
Plants restore something that breathing animals and burning candles remove. This gas was later named "oxygen".

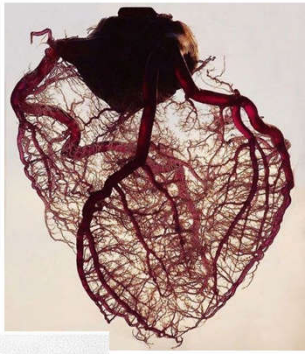


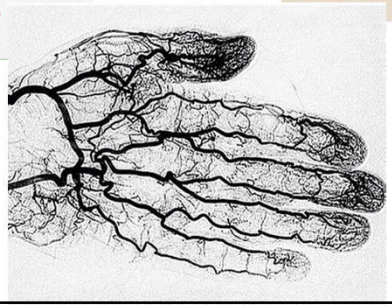


How is everything transported?

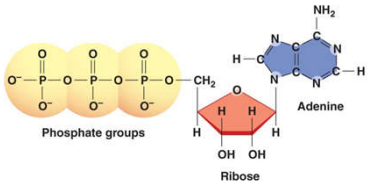


Some organs need more energy





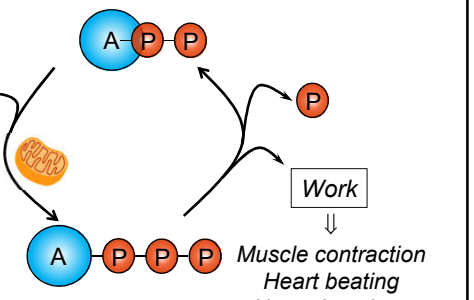
Food is converted into energy currency



ATP is universal source of energy occurring in all cell types. In animals it is produced during the degradation of foodstuff in mitochondria.

Food
(sugars, fats, proteins)
+
Oxygen

⇒ *energy*



Work

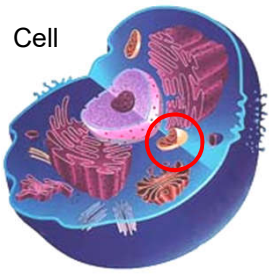
⇓

Muscle contraction
Heart beating
Nerve impulses
Tissue growth
DNA and protein synthesis
Cell division
Transport
Detoxification

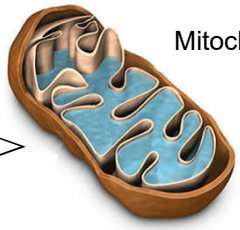
ATP is formed and broken at a rate of around 9×10^{20} molecules per second, equivalent to a turnover rate of ATP of 65 kg per day

Where is ATP synthesized?

Cell



Mitochondria



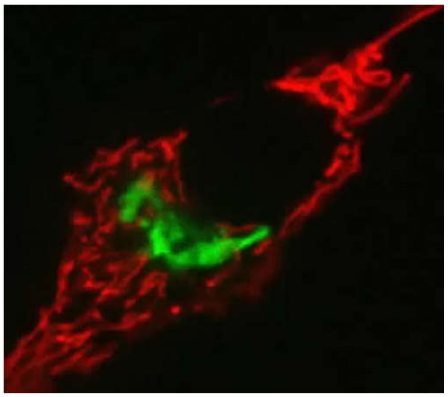
95% of ATP is generated here

All oxygen we breathe in is consumed by mitochondria (~400 L per day)

~10^{15} mitochondria in our body ~ 10% of the body weight

Mitochondria contains its own DNA

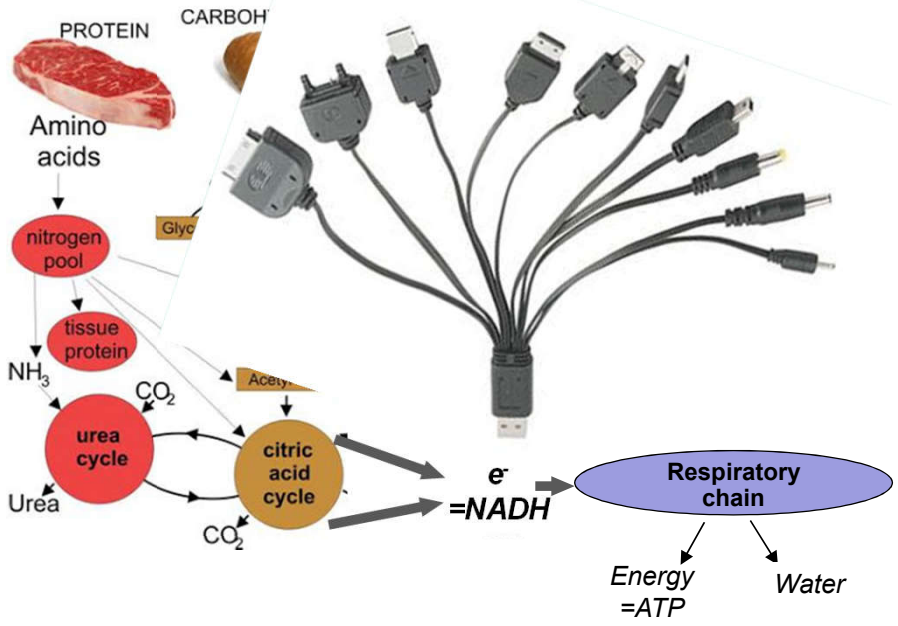
There is no single mitochondrion, but mitochondrial dynamic network



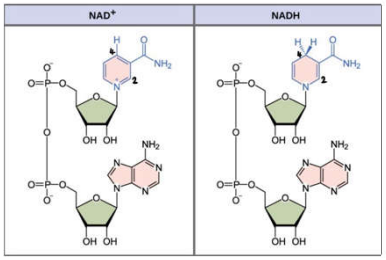
Mitochondria are red

Mitochondria are green

Unification of substrate

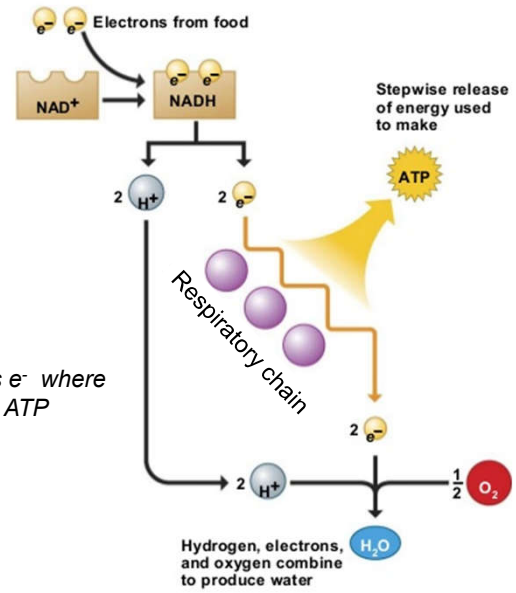


Eventually electrons end up on NADH

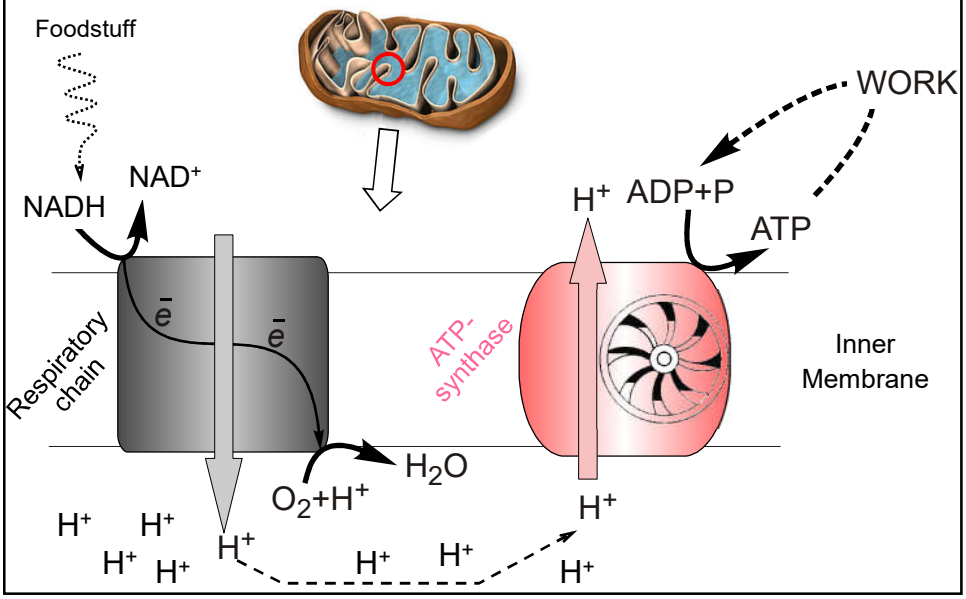


$NAD^+ + 2e^- + H^+ \leftrightarrow NADH$

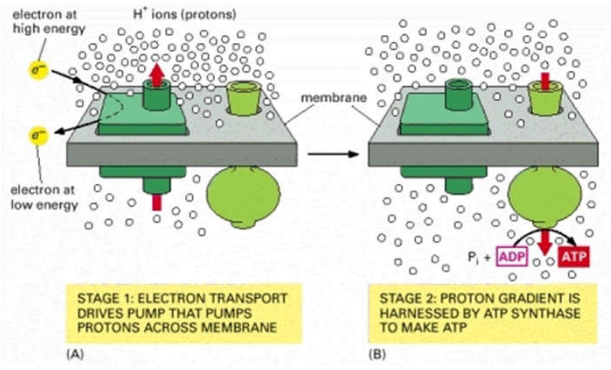
NADH=Electron shuttle which deliver s e^- where their energy can be converted to ATP



Mitochondria couple NADH oxydation by oxygen with ATP synthesis



Chemiosmotic theory



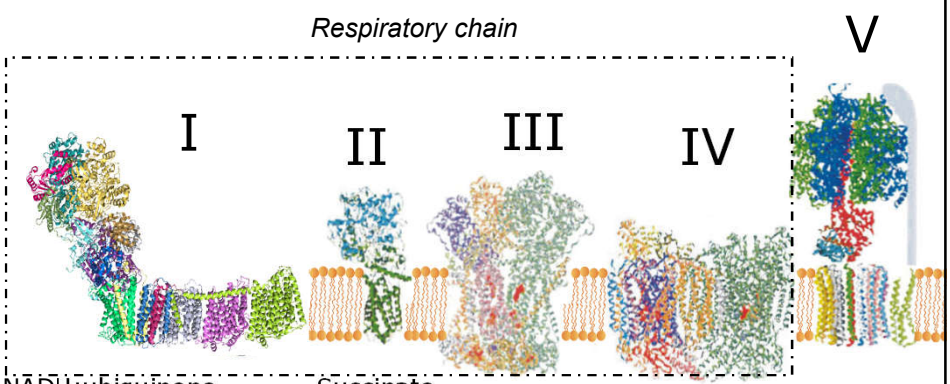
Peter Mitchell

Nobel Prize 1978

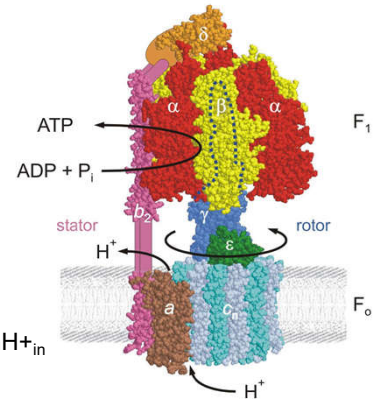
Electron transfer along respiratory chain is coupled with proton translocation from one side of the membrane to another.

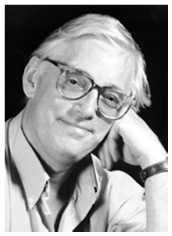
The difference in concentration of protons can drive special molecular motor – ATP synthase.

Structure of mitochondrial respiratory chain complexes and ATP-synthase



ATP synthase





John Walker
Nobel prize 1997

$ADP + P_i + nH+_{out} \leftrightarrow ATP + nH+_{in}$

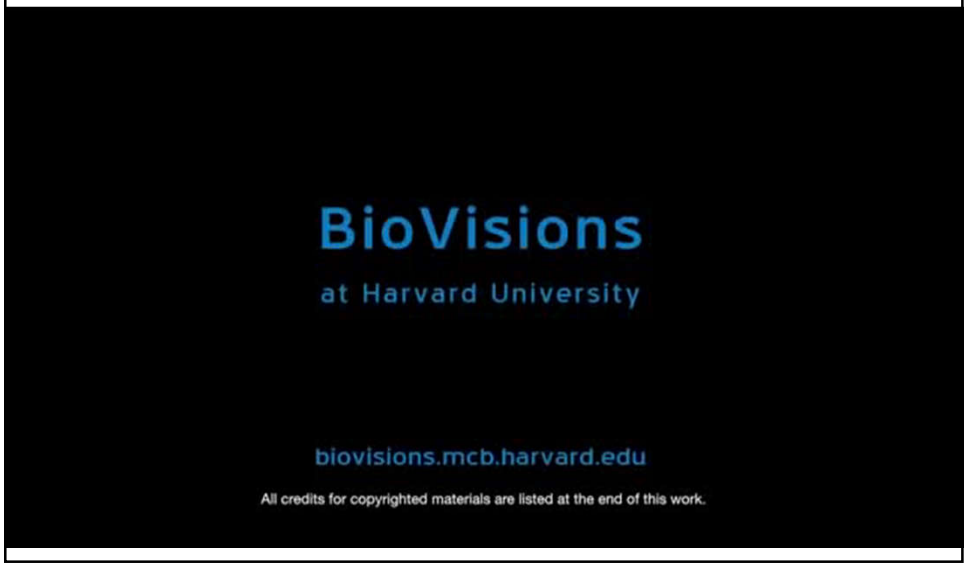
Proton flow through membrane part is coupled with ATP synthesis in the F_1 part

8-10H^+ per 3 molecules of ATP

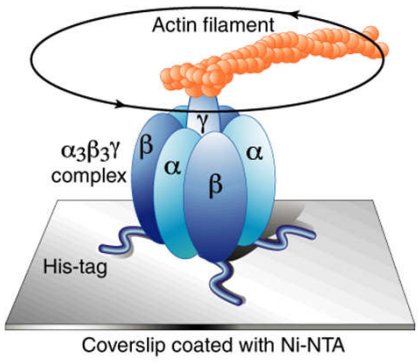
Reversibility: proton flow in one direction drives ATP-synthesis from ADP and P

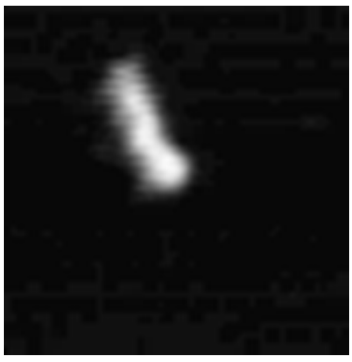
ATP hydrolysis drives proton pumping in the other direction

Mitochondrial ATP-synthase is a designed nanomotor



ATP synthase





ATPase was attached to a glass cover slip and a long filament was attached to the shaft top.

Mitochondria are main source of energy production in a cell

Most likely mitochondria are responsible for production of ~95% of our ATP.

Inner mitochondrial membrane ~14000m^2 ~two football pitch

During respiration in mitochondria oxygen undergoes 4-electron reduction:

$$O_2 + 4e^- + 4H^+ \rightarrow 2H_2O$$

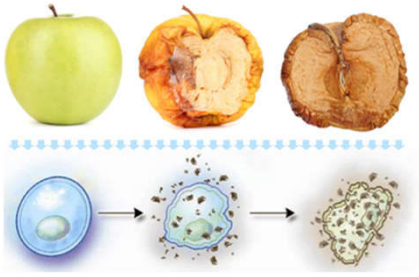
but...

Oxygen can be reduced in a different way

Mitochondria are main source of energy production in a cell, but...

During degradation of food and respiration there is a formation of special byproducts of oxygen– so called Reactive Oxygen Species or Free Radicals

These molecules want to react with everything and damage all cells!



Reactive oxygen species (ROS)

One electron reduction of molecular oxygen

$O_2 + 1e^- \rightarrow O_2^{\cdot -}$ — Superoxide radical (photochemistry or electron leak)

Dismutation of superoxide radical

$O_2^{\cdot -} + O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2$ — Hydrogen peroxide (hair lightening)

Transition metal ions catalyse Fenton reaction

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\cdot}OH$ — Hydroxyl radicals (house bleach)

Small fraction of electrons can "leak" from the respiratory chain and other enzymes. Some of oxygen molecules can be reduced to form "free oxygen radicals" or reactive oxygen species (ROS) – these molecules want to accept or to release electrons to go to the lower energy state ⇒ they are highly reactive and can interact with other molecules in a cell – proteins, DNA and membrane lipids – and damage them

Sources of free radicals

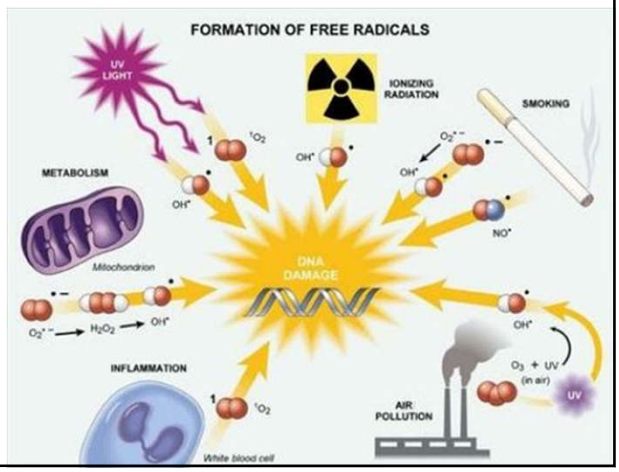
•Leak from mitochondria and other systems (especially when the diet is bad)

•Toxic compounds (sulfa drugs, antimalarial drugs, anticancer drugs=chemotherapy)

•UV light from the Sun

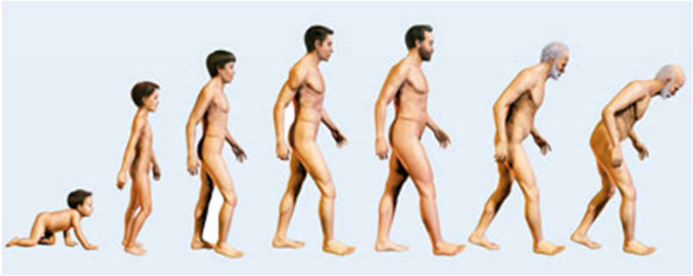
•Ionising radiation

•Smoking



How could mitochondria kill us at the end?

Mitochondrial free radical theory of ageing



Mitochondria make radicals as a byproduct of energy metabolism

⇓

Slowly, radicals damage mitochondria and mitochondrial DNA

⇓

More mutations occur and they slowly accumulate

⇓

Mitochondria cannot produce enough energy

⇓

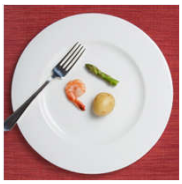
Energy crisis and DEATH ☠✞

Denham Harman

How to fight death and live longer?

Molecules that can scavenge free radicals are called antioxidants (found in fruits and vegetables or manufactured)
??

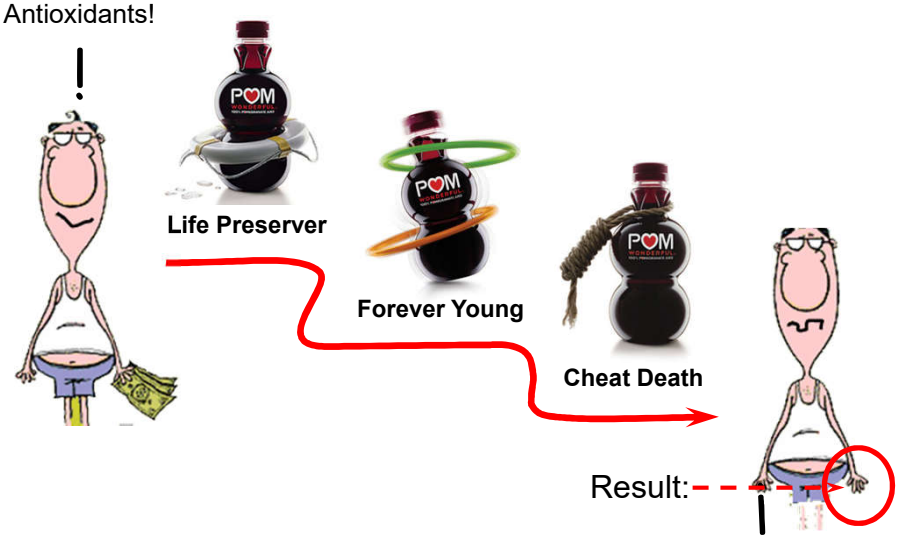
Caloric restriction after 30-40 yo – the less food is going through the mitochondria, the less leak of oxygen radicls would happen



Physical exercises strongly stimulate natural mechanisms of radicals detoxification, new neurons formation , etc

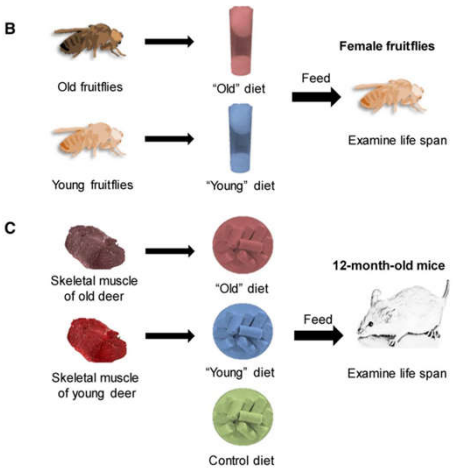
Antioxidants?

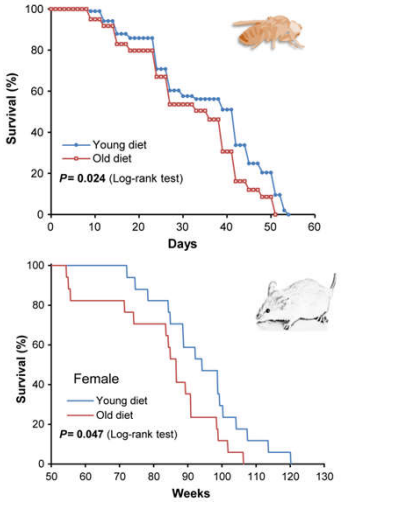
Antioxidants!



No convincing evidence that antioxidants can prolong life
(may be they should be targeted to mitochondria!?)

Diet?





SCIENCE ADVANCES | RESEARCH ARTICLE

BIOCHEMISTRY

Age-associated molecular changes are deleterious and may modulate life span through diet

Sang-Goo Lee,[1,2] Alaattin Kaya,[1] Andrei S. Avanesov,[1] Dmitriy I. Podolskiy,[1] Eun Ju Song,[3,4] Du-Min Go,[3] Gwi-Deuk Jin,[3] Jae Yeon Hwang,[3] Eun Bae Kim,[5,7] Dae-Yong Kim,[3] Vadim N. Gladyshev[1]*

Diet is important!

Myths about diets

Hay diet – combining food in three groups: alkaline, acidic, and neutral
Raw food diet (food should be uncooked)
Paleodiet = caveman diet
Detox (accumulated waste removal)
Zero calories food
Goji berries, vinegar, lemon juice + olive oil – cleans your guts
Metabolism boost pills – "burn your fat" food supplements

NO SCIENTIFIC EVIDENCE
NO RANDOMIZED COHORT STUDIES
YET?

Vegetarian diet

WHO: Vegetarian diet is acceptable for adults if supplements are added

Vitamin B12 =cobalamin
Essential amino acids
Creatine (ATP-depot)
Polyunsaturated fatty acids
Iron and zinc.

The American Journal of
CLINICAL NUTRITION
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Mortality in vegetarians and comparable nonvegetarians in the United Kingdom[1–3]

*Paul N Appleby, Francesca L Crowe, Kathryn E Bradbury, Ruth C Travis, and Timothy J Key**

60,000 people were involved

In conclusion, our results suggest that United Kingdom–based vegetarians and comparable nonvegetarians (including people who eat fish but not meat and those who eat meat <5 times per week on average) have similar all-cause mortality. The differ-

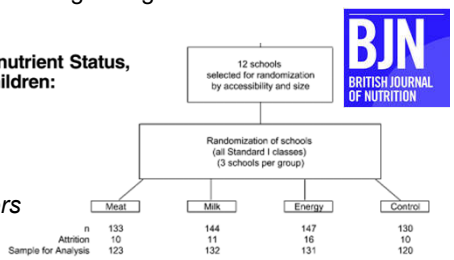
Vegetarian diet for kids

Vegan and vegetarian diet for young children and adolescent
Good or Bad?

There are direct and indirect evidence that vegetarian and vegan diets may be associated with serious risks for growing children.

Animal Source Foods Improve Dietary Quality, Micronutrient Status, Growth and Cognitive Function in Kenyan School Children: Background, Study Design and Baseline Findings[1,2]

Improved cognitive performance and academic test scores, increased physical activity and leadership and initiative behaviors in the "Meat" group



BJN BRITISH JOURNAL OF NUTRITION

The American Journal of CLINICAL NUTRITION

Signs of impaired cognitive function in adolescents with marginal cobalamin status[1–3]

Marieke WJ Louwman, Marijke van Dusseldorp, Fons JR van de Vijver, Chris MG Thomas, Jørn Schneede, Per M Ueland, Helga Refsum, and Wija A van Staveren

Where to get information

www.pubmed.ncbi.nlm.nih.gov – Library of scientific peer-reviewed publications

www.cdc.gov - Center for disease control and prevention, USA

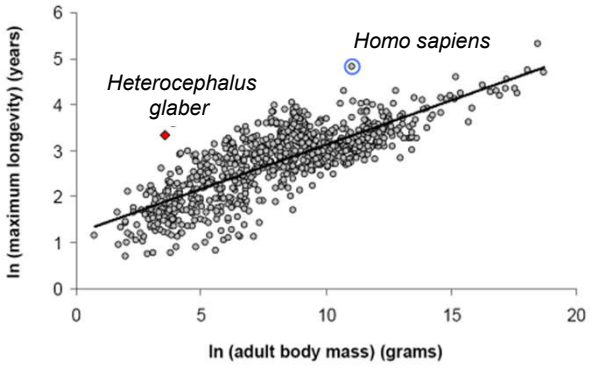
www.patient.info - Health information, UK

www.fda.gov - Food and Drug Administration, USA

Where to look for an answer?

Maybe look at long-living animals?

Relationship between maximum longevity and adult body mass



AnAge: The Animal Ageing and Longevity Database

Ugly exception: Naked rat mole

Naked mole rats live ~30 years (not 3-4 years as other rodents)

They are mammals but their temperature is not constant

Has exactly 100 hairs

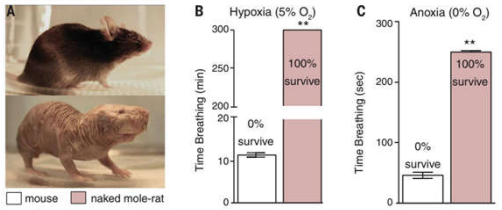
Underground colonies are organized like an bees or ants community with a single breeding queen and workers and soldiers

Very different oxygen metabolism

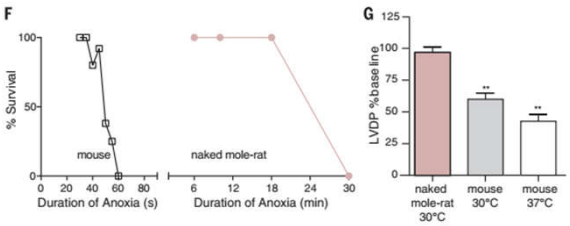
Science

Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat

Thomas J. Park,[1*†] Jane Reznick,[2†] Bethany L. Peterson,[1] Gregory Blass,[1] Damir Omerbašić,[2] Nigel C. Bennett,[2] P. Henning J. L. Kuich,[3] Christin Zasada,[4] Brigitte M. Browe,[1] Wiebke Hamann,[3] Daniel T. Applegate,[1] Michael H. Radke,[5,6] Tetiana Kosten,[2] Heike Lutermann,[2] Victoria Gavaghan,[1] Ole Eigenbrod,[2] Valérie Bégay,[2] Vince G. Amoroso,[1] Vidya Govind,[1] Richard D. Minshall,[7] Ewan St. J. Smith,[6] John Larson,[6] Michael Gotthardt,[5,6] Stefan Kempa,[4] Gary R. Lewin[2,10*]

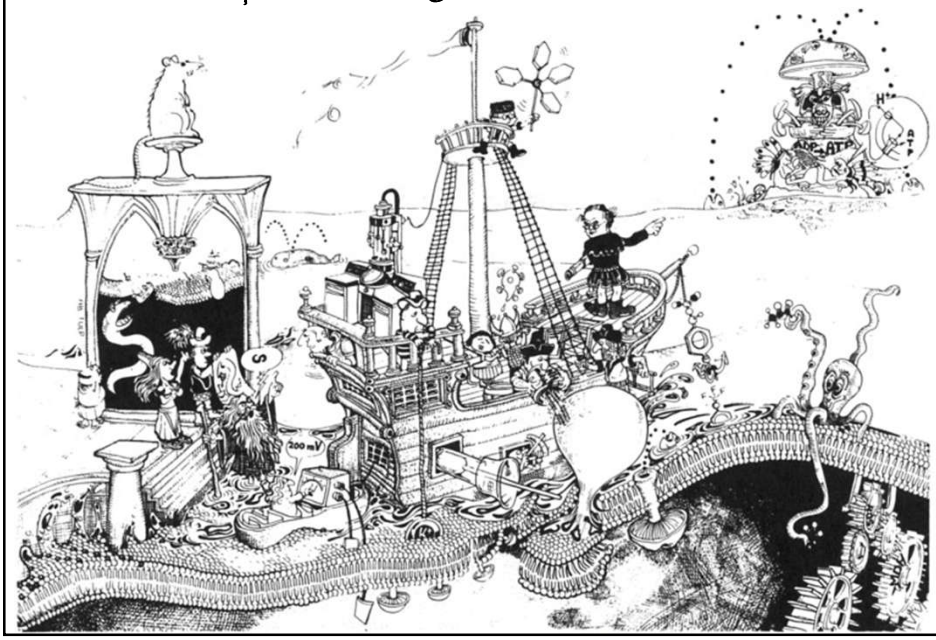


Oxygen metabolism is a key!



Ugly exception: Naked rat mole

Peter Mitchell sets sail for the Chemiosmotic New World,
despite dire warnings that he will be consumed



Thank you!

Questions?

www.complexi.org

Truth about diets

Balanced diet – meet, fish, milk, grains, fruits and vegetables

It is better to eat less than more

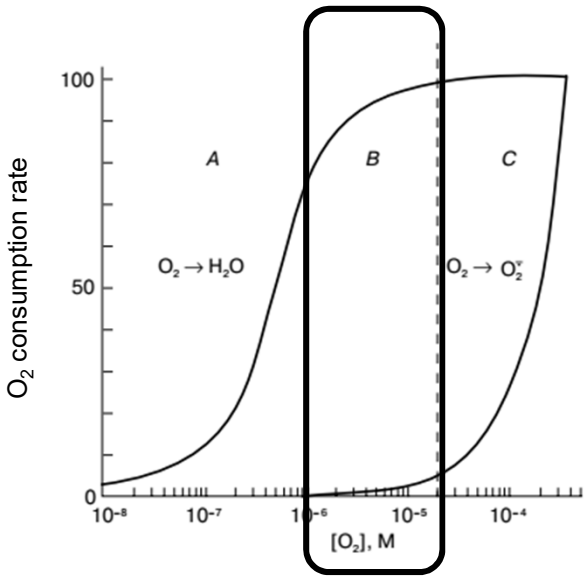
Avoid regular consumption of fizzy drinks with a lot of sugar (Coke, Pepsi, etc)

Reduce salt consumption

Avoid Trans-fat (partially hydrogenated oils) – in many cookies, doughnuts, cakes, frozen pizza, butter-like spreads

Most likely red processed meat should be limited

At what oxygen concentration do we live?



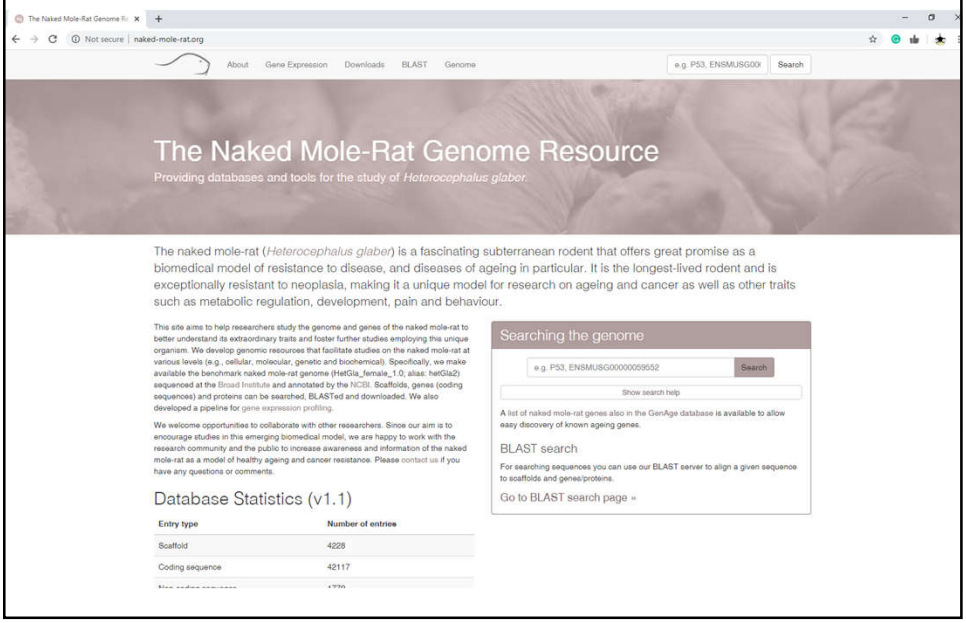
Detox and cleanse

"cleanse your system and whisk away the polluting nasties and toxins"

NOT TRUE!
No toxins were shown by these companies
Cannot remove what is not there

A colony of mole-rats at the University of Cambridge, UK

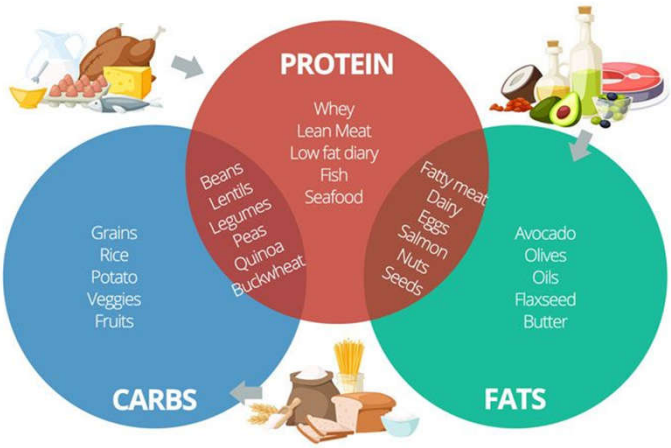
Genome is known = we know all the genes (DNA sequence)



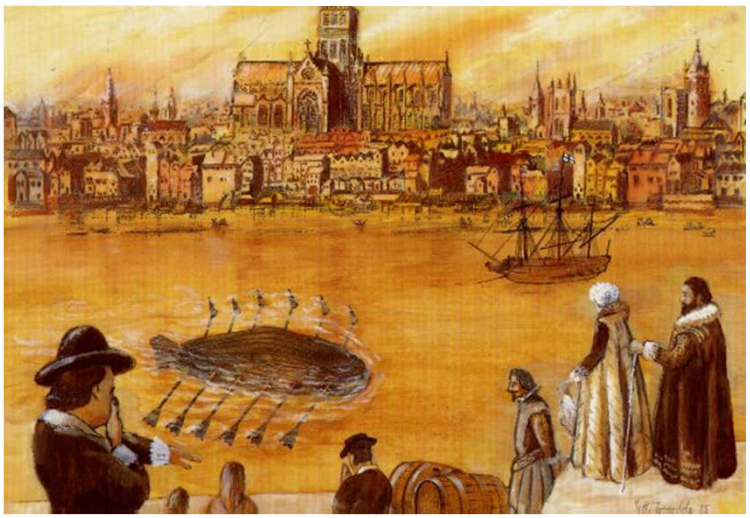
What do we eat?

Chocolate = fats + sugars
Steak = proteins + fats
Beans = proteins + sugars

Burger =proteins + fats + sugars

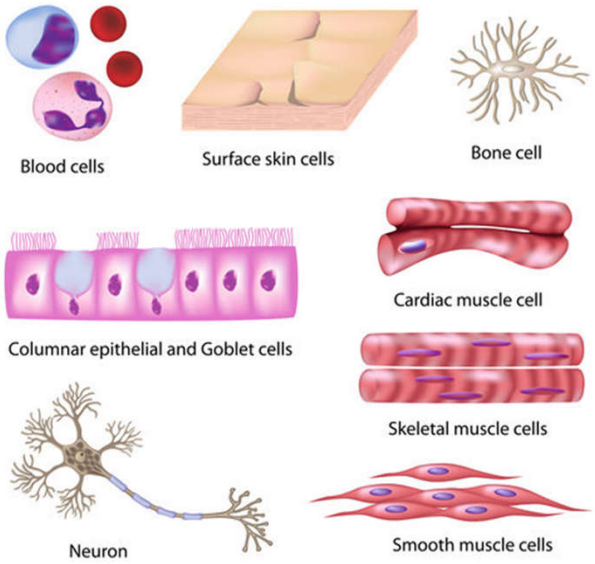


Cornelis Drebbel (1620)
Netherlands



Production of “breathable gas” for the first submarine
150 years before Priestley!

Our body is composed of different cells and every cell needs energy!



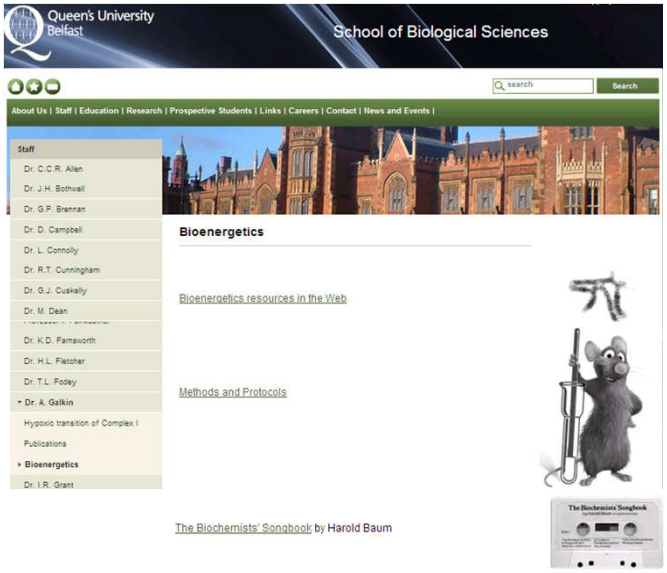
How much energy is in our food?

For 10-13 yo
1600-1800 calories/day

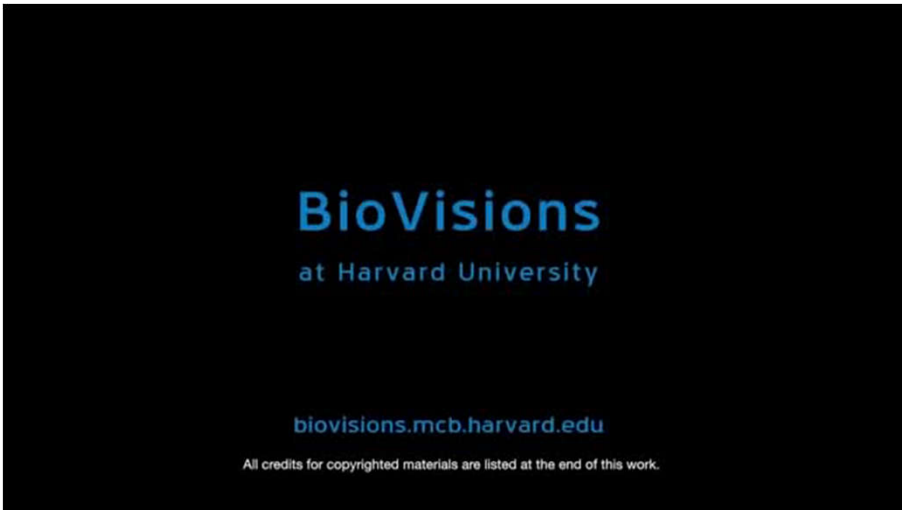
No such thing as a ~~negative calorie food~~

More stuff and bioenergetics links

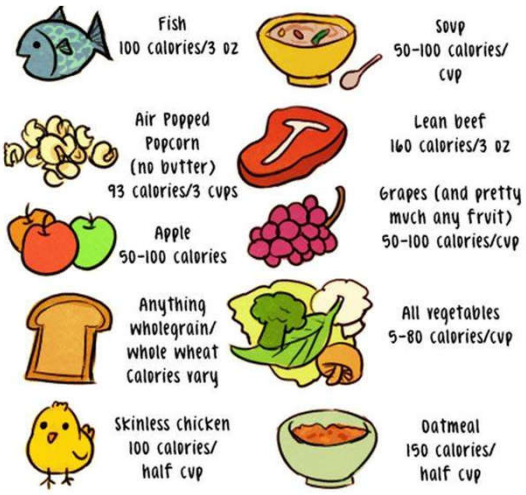
http://go.qub.ac.uk/Galkin



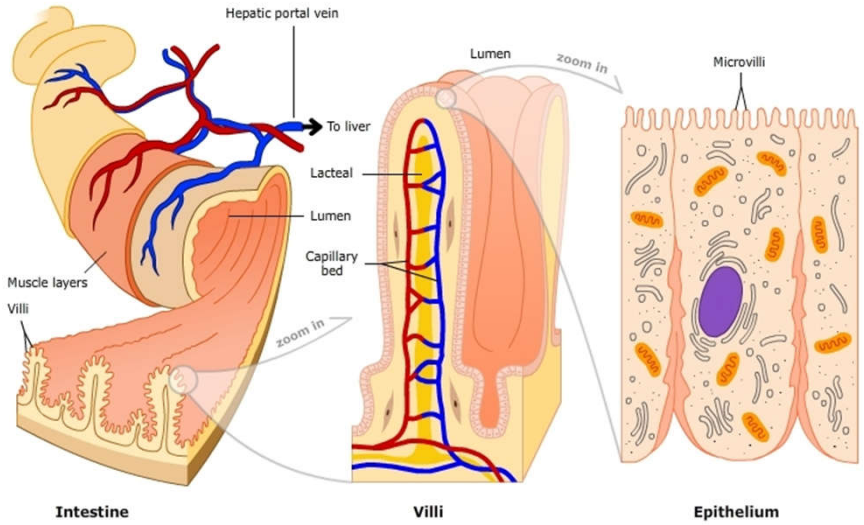
Mitochondria couple food molecules degradation and oxygen consumption with ATP synthesis



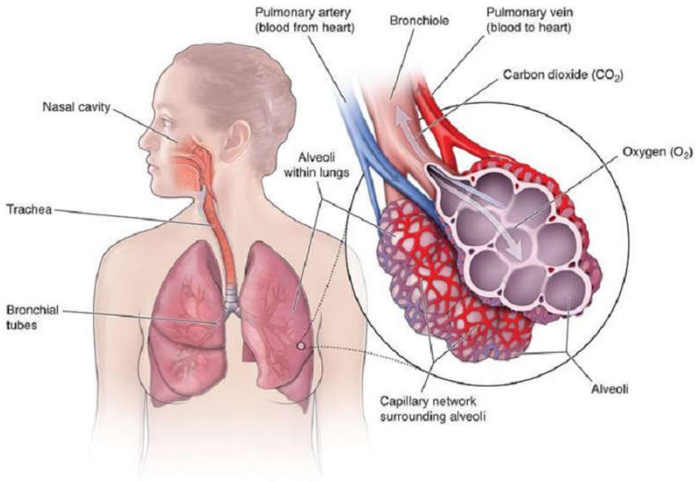
How do we measure energy in food?



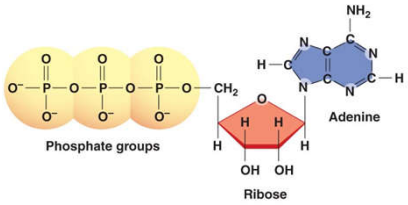
How does everything go into blood?



What is the source of oxygen in the blood?

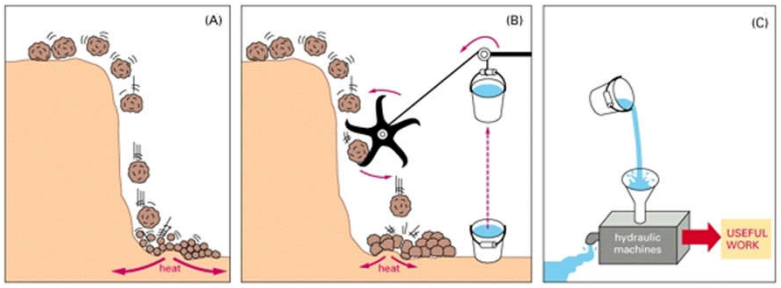


A bit of chemistry



ATP is regarded as a universal source of energy occurring in all cell types. In animals it is produced during the degradation of foodstuff.

$$ATP \rightarrow ADP + P_i + \textit{energy}$$



Burning (oxidation) of food to CO_2 and H_2O produces heat only

Cells can store energy during food oxidation in form of ATP

ATP is used to drive any cellular processes