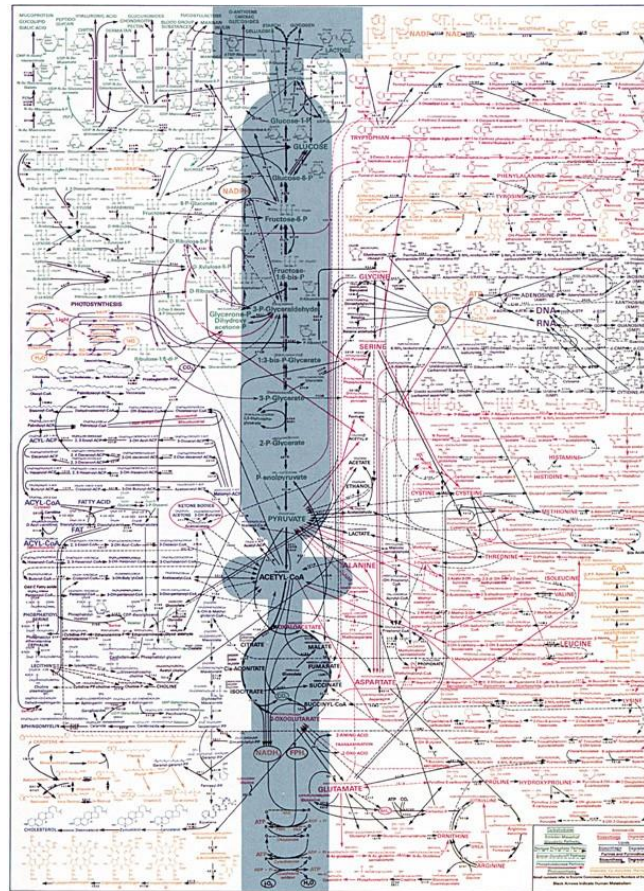
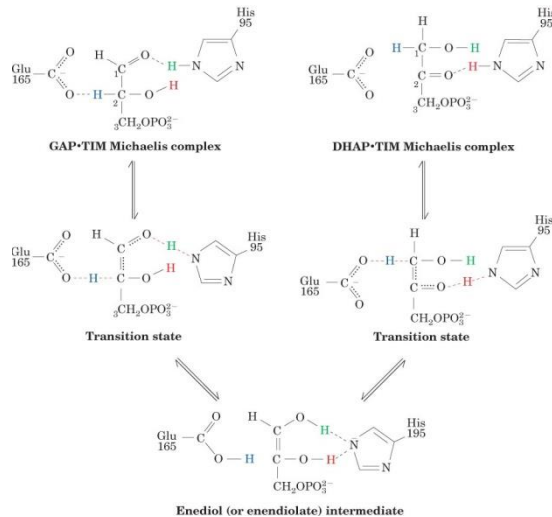
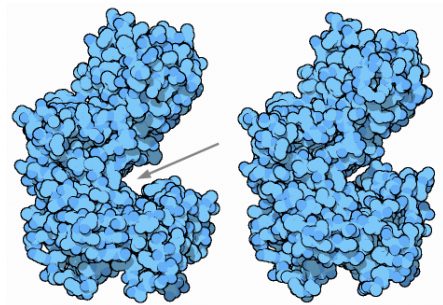
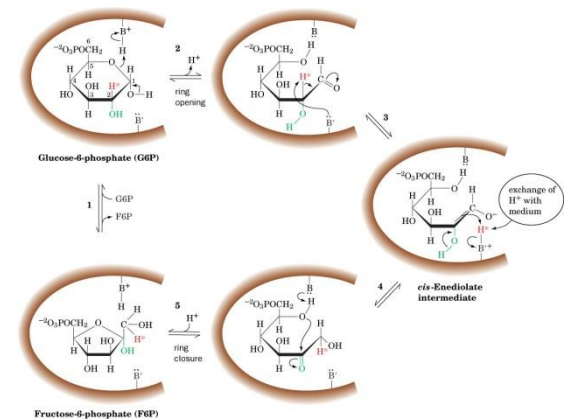
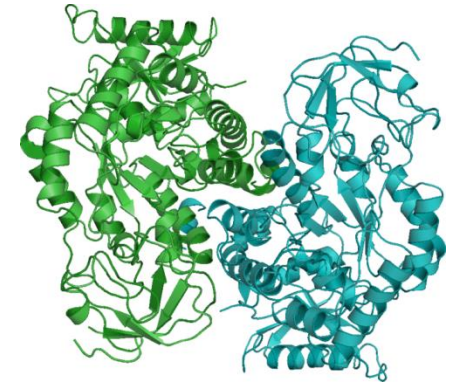


Welcome to Biochem 3050 / Biology 3010: Enzymes and Metabolism



Designed by Donald Nicholson. Published by BDH, Ltd., Poole 2, Dorset, England



The Syllabus 2024

York University

Department of Chemistry and Department of Biology

Advanced Biochemistry, Winter 2024

Biology 3010 3.0 / Chemistry 3050 3.0 / Biochemistry 3010 3.0

Instructor: Derek Wilson
Office: LSB331C
email: dkwilson@yorku.ca

Lectures: M/W/F 9:30 – 10:30
M/W/F Steadman Lecture Hall D

Office Hours: Monday, Wednesday, and Friday 10:30-11:30 LSB331C

Prerequisites: SC/BIOL 2020 4.0 or BCHM 2020 4.0 or SC/CHEM 2050 and SC/CHEM 2020 6.0.

Calendar Description: A detailed discussion of enzyme structure and function. The chemistry and metabolism of biological molecules. Metabolic regulation at the level of enzyme activity. Knowledge of general concepts of metabolism and of basic aspects of enzyme structure and function is assumed.

Text*: I recommend 'Biochemistry' Donald Voet and Judith Voet, any edition, John Wiley & Sons, Inc. publishers.

* This text is recommended, but **not** required. *Almost All* of the material will be available in any recent, university level biochemistry text and in the (online) lecture notes.

Library Material: A number of biochemistry textbooks are on reserve in the Steacie Library including...

Lehninger Principles of Biochemistry, Nelson & Cox.

Biochemical Calculations, Segel.

Biochemistry, Horton, Moran, *et al.*

Biochemistry, Stryer.

Introduction to Protein Structure, Branden & Tooze.

Website: Course material can be accessed by linking from <http://www.yorku.ca/dkwilson>. All documents pertaining to the course will be posted.

Marking scheme:

Midterm exam 1 - 30% February 16th

Midterm exam 2 - 30% March 22nd

Final exam - 40%

Grading: The grading scheme for the course conforms to the 9-point grading system used in undergraduate programs at York (e.g. A+=9, A=8, B+=7, B=6, C+=5, C=4, D+=3, D=2, E=1, F=0). A letter grade for the course will be assigned based on the final percentage grade (A+=90-100, A=80-89, B+=75-79, B=70-74, C+=65-69, C=60-64, D+=55-59, D=50-54, E=40-49, F=0-39).

Academic Honesty:

York students are required to maintain high standards of academic integrity and are subject to the **Senate Policy on Academic Honesty**: (<https://www.yorku.ca/secretariat/policies/policies/academic-honesty-senate-policy-on/>)

Students may also review York's 'SPARK' materials on the **Academic Integrity**: (<https://spark.library.yorku.ca/academic-integrity-what-is-academic-integrity/>)

Access/Disability: Students with disabilities, including physical, medical, systemic, learning and psychiatric disabilities may need accommodation in exam requirements. Students are encouraged to notify the course director and to seek advice from the Counselling and Development Centre. Failure to notify the course director of your needs in a timely manner may jeopardize the opportunity to arrange for academic accommodation.

Notes:

(1) **E-mail policy:** All emails must include the name of the sender. It is preferred that your@yorku.ca email address be used. Messages from accounts like bleh@hotmail.com or similar may not receive a reply, probably because the email will be sent to my spam box.

(2) **Test Marking:** Test grades are normalized to test difficulty by 'bumping' the entire class by an amount that makes the highest grade 100% (*i.e.*, if the highest grade is a 98%, then everyone's grade will be increased by 2%).

(3) **Missed tests and exams:** There **may or may-not** be a make-up for missed midterm tests/exams. If not, for each missed midterm (with appropriate documentation) the value of the test will be added to the remaining midterm and final exam (for a missed midterm exam 1) or to the final exam (for a missed midterm exam 2).

(4) **Re-grade policy.** If, after tests are graded and returned, there is a question concerning the grading of a test, the *entire* test should be returned. The *entire* test may then be re-graded. All requests for re-grading must be made in writing and must be submitted to Dr. Wilson no later than the end of lecture 1 week after the test is returned to the class. The request should identify the question of concern and briefly explain the marking error and/or scientific reason why your answer merits further consideration.

The Syllabus 2024

Course Outline (Approximate!!)

Week 1 (Jan 8th - 12th): *Introduction. What is this thing called 'metabolism'? WHY??*

Week 2 (Jan 15th - 19th): *Proteins – Amino acids to Peptides to Proteins*

Week 3 (Jan 22nd – 26th): *Enzymes and Protein Structure*

Week 4 (Jan 29th – Feb 2nd): *Enzyme Regulation and Mechanisms – Kinetics and Thermodynamics*

Week 5 (Feb 5th – 9th): *Enzyme Regulation, Enzyme dynamics and Function*

Week 6 (**Feb 12th – 16th**): *Enzyme Function, Review, **Mid-Term!** (Feb 16th)*

Reading Week (Feb 19th – 23rd)

Week 7 (Feb 26th – March 1st): *Metabolic Pathways, Enzymes and Energy Metabolism*

Week 8 (March 4th – March 8th): *Metabolism of Fatty Acids*

Week 9 (March 11th – March 15th): *Metabolism of Nucleotides and Amino Acids*

Week 10 (**March 18th – March 22nd**): *Metabolism, Review, **Mid Term!** (March 22nd)*

Week 11 (March 25th – March 29th): *Metabolism of Iron/Calcium*

Week 12 (April 1st - April 5th): *Metabolism of Caffeine, Metabolic Poisons*

Week 13 (April 8th): *Exam prep*

Extra, maybe!: *Evolution of Metabolism*

Metabolism – What is it?

Websters – ‘the sum of the processes in the buildup and destruction of protoplasm; *specifically* : the chemical changes in living cells by which energy is provided for vital processes and activities and new material is assimilated b: the sum of the processes by which a particular substance is handled in the living body c: the sum of the metabolic activities taking place in a particular environment <the *metabolism* of a lake>’

Websters Etymology - International Scientific Vocabulary, from Greek *metabolē* change, from *metaballein* to change, from *meta-* + *ballein* to throw — more at devil
↖
?

Wikipedia – Metabolism is the set of chemical reactions that occur in living organisms in order to maintain life

Metabolism Allows:

- Collection/Storage of Energy
- Maintenance of pH, temperature, salt conditions
- Fabrication of big, low entropy molecules

Metabolsim – Why?

Big Questions

How did metabolism appear? What was the earliest metabolism?

Metabolic networks – where are the weak points and why are they there?

Can metabolic control be reduced to a small number of archetypes?

Applications

- Higher/faster/stronger



- Metabolic diseases / disorders / syndromes: Diabetes, Wilson's disease, many, many others

- Metabolic poisons



: Cyanide, 2,4-Dinitrophenol, Oligomycin, many, many others

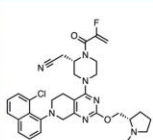
- *Drug metabolism*

- Nutrition

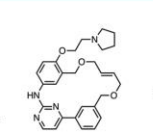
Metabolsim – Why Part Deux

2022 Novel Small Molecule Drug Approvals

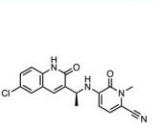
Oncology (5)



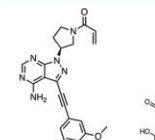
Krazati, KRAS^{G12C} inhibitor
(adagrasib)
for KRAS^{G12C} + NSCLC after at least one prior systemic therapy
600 mg orally BID
MIRATI



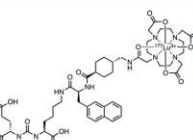
Vonjo, JAK2/IRAK1 inhibitor
(pacritinib)
for myelofibrosis
200 mg orally BID
CTI BIOPHARMA



Rezidhia, IDH1 inhibitor
(olutasidenib)
for R/R AML with susceptible IDH1 mutation
150 mg orally BID
RIGEL

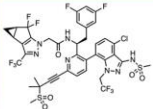


Lytgo, irreversible FGFR1-4 inhibitor
(futibatinib)
for ICCA with FGFR2 rearrangements
20 mg orally QD
TAHO

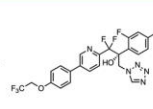


Pluvicto, PSMA-targeted radiotherapy
(lutetium ¹⁷⁷Lu vipivotide tetraxetan)
for PSMA-positive prostate cancer
7.4 GBq (200 mCi) IV Q8W up to 6 doses
NOVARTIS

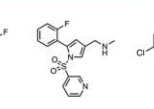
Infectious Diseases (3)



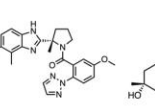
Sunlenca, HIV-1 capsid inhibitor
(lenacapavir)
for multidrug resistant HIV-1 infection
927 mg SC Q6M after loading
GILEAD



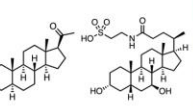
Vivipao, antifungal (CYP51 inhibitor)
(oteseconazole)
for RVVC in non-reproductive females
600-150 mg oral 11 week regimen
MYCOVIA



Voquezna, K⁺/H⁺-ATPase potassium channel blocker
(vonoprazan*, amoxicillin, and clarithromycin)
for H. pylori infection
20 mg BID for 14 days in combo
TAKEDA



Quvivra, OX1/2 dual antagonist
(daridorexant)
for insomnia
25-50 mg orally QD
IDORSIA

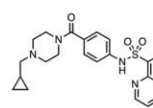


Zilaymo, GABA_A PAM
(ganaxolone)
for seizures in CDKL5 deficiency disorder
6 mg/kg orally TID
MARINUS

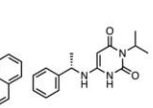


Relyvrio
(sodium phenylbutyrate and taururacil*)
for AAS
1 g orally daily
AMLYX PHARMACEUTICALS

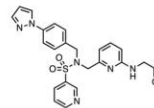
Other (5)



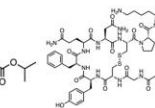
Pyrukynd, PK activator
(mitapivat)
for hereditary anemia in PK deficiency hematology
5 mg orally QD
AGIOS



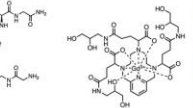
Camzyo, myosin inhibitor
(mavacamten)
for obstructive HCM cardiomyopathy
5 mg orally QD
BMS



Omilont, EP2 receptor agonist
(omidenepag isopropyl ophthalmic solution)
for open-angle glaucoma and ocular hypertension ophthalmology
topical, one drop in affected eye
SANTEN

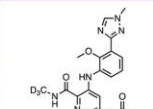


Terlizav, vasopressin receptor agonist
(terlipressin)
for hepatorenal syndrome in patients with reduced kidney function hepatology
starting dose: 0.85 mg IV Q8h on day 1-3
MALLINCKRODT

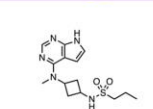


Elucirem, gadolinium-based contrast agent
(gadopicolone)
for MRI imaging of lesions with abnormal vascularity diagnostic
0.05 mmol/kg IV infusion
GUERBT

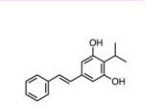
Dermatology (3)



Sotyktu, TYK2 allosteric inhibitor
(deucravatinib)
for moderate to severe plaque psoriasis
6 mg orally QD
BMS



Cibinqo, JAK1 inhibitor
(abrociclib)
for refractory atopic dermatitis
100 mg orally QD
PFIZER



Vtama, AHR agonist
(tapinarof)
for plaque psoriasis
1% cream topically QD
DERMAYANT SCIENCES

drughunter.com

*novel component
This poster is for informational purposes only and is not intended for medical use.

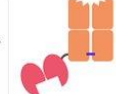
drug
hunter

2022 Novel Large Molecule Drug Approvals

Oncology (6)



Elahere, FRA-binding maytansinoid ADC
(invetumumab sarvatamab-gym)
for ovarian cancer resistant to platinum
6 mg/kg IV infusion Q2W
IMMUNOGEN



Kimmtrak, bispecific gp100 peptide-HLA-directed CD3 T cell engager
(tebentafusp-tetbi)
for uveal melanoma
starting dose 20 µg IV infusion
IMMUNOCORE



Opdivoo, Lag-3 checkpoint inhibitor
(nivolumab (PD-1) and relatlimab-rmbx*)
for melanoma
480 mg nivolumab and 160 mg relatlimab IV infusion Q4W
BMS



Tecvayli, IBCMA-directed CD3 T-cell engager
(teclistamab-cvqi)
for SLL/CLL
starting dose 0.06 mg/kg SC
JANSSEN



Lunsumio, CD20xCD3 T-cell engager
(lunaseumab-cvqi)
for B19 follicular lymphoma
starting dose 1mg IV infusion
ROCHE



Imjudo, CTLA-4 checkpoint inhibitor
(tremelimumab)
for hepatocellular carcinoma
300 mg IV transfusion Q4W
of nivolumab
ASTRAZENECA

Hematology/Oncology (1)



Rovelon, rhG-CSF (teopagranin)
for infection-related neutropenia in cancer
10 mg SC daily per chemotherapy cycle
SPECTRUM PHARMACEUTICALS



Enjaymo, complement component (C3a) inhibitor
(c3anemab-jmnl)
for cold agglutination disease
starting dose 6.5 g IV infusion QW
SANOFI

Ophthalmology (1)



Vabysmo, VEGF and Ang-2 inhibitor
(faricimab-ovrl)
for neovascular AMD and diabetic macular edema
6 mg intravitreally Q4W
GENENTECH

Rare Disease (1)



Xenpazyme, acid sphingomyelinase replacement
(olipodase alfa)
for Acid Sphingomyelinase Deficiency
starting dose 20 mg/kg IV infusion
SANOFI



Amvuttra, TTR siRNA
(vuttra)
for polyneuropathy of hereditary transthyretin-mediated amyloidosis
25 mg SC QM
ALNYLAM PHARMACEUTICALS



Briumvi, anti-CD20 mAb
(briatimab)
for relapsed MS
starting dose 150 mg IV infusion
TO THERAPEUTICS

Dermatology (3)



Spvegro, IL-36 receptor antagonist
(spesolimab-sbz)
for psoriasis vulgaris
single dose 450 mg/7.5 mL solution IV
BOEHRINGER INGELHEIM

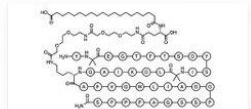


Daxxify, ACh release inhibitor
(botulinum toxin formulation)
(daxibotulinumab-dk-lav)
for moderate to severe glabellar lines
0.1 mL, 94 into five sites
RENVANCE THERAPEUTICS



Nexobrid, proteolytic enzymes enriched in bromelain
(necanase-bocbi)
for removing scabrous caused by thermal burns
2 g per 1% total body surface area
MEDWOUND

Endocrinology (2)



Mounjaro, GIP and GLP-1 receptor agonist
(tirzepatide)
for diabetes
2.5 mg SC QW
ELI LILLY



Tzield, CD3-directed immunosuppressant
(teplimab-mw)
to delay the onset of Stage 3 Type 1 diabetes
IV infusion QD over 14 d
PROVENTION BIOSANOFI



visit for more information on
<https://drughunters.com/2022mda>
each drug including:
• how they were discovered
• how they work
• how they differentiate
• ...and more

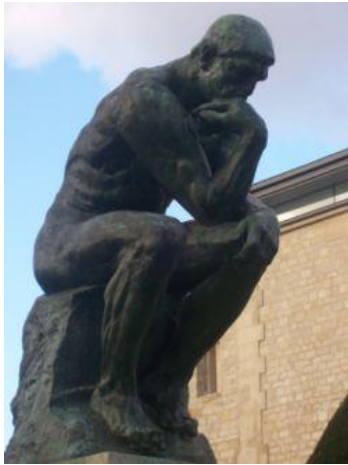
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*novel component
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Course Outline

Who started thinking about metabolism first?



Paris



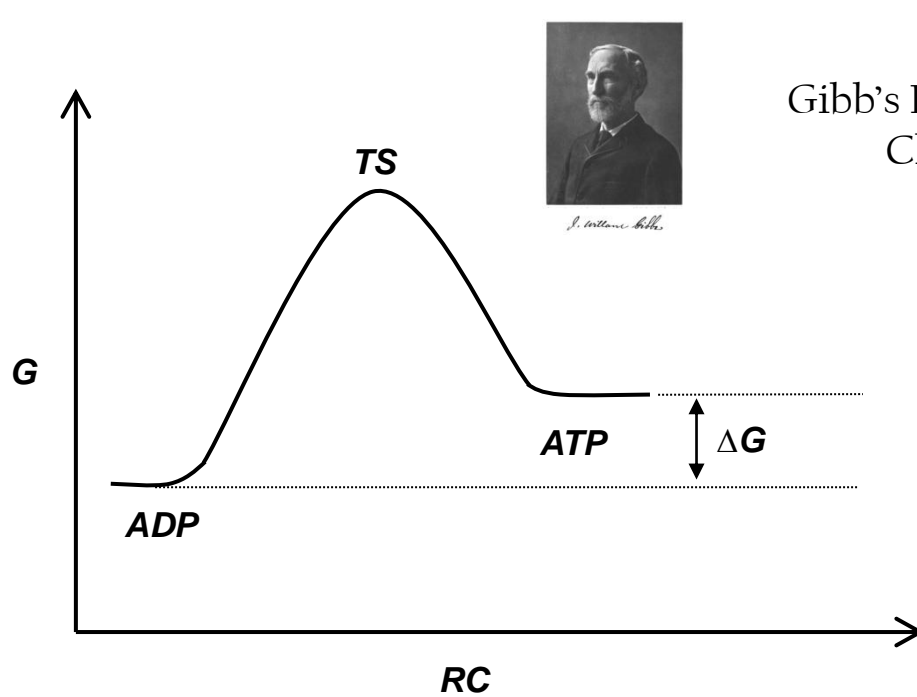
Washington



Kyoto

Metabolism, Chemically

The Challenge: Most of the Processes Required to Sustain Life are *Endergonic*



Gibb's Free Energy Change

Enthalpy Change (energy)

Entropy Change (degrees of freedom)

$$\Delta G = \Delta H - T\Delta S$$

$-\Delta G$:  *Exergonic*. Product is favored

$+\Delta G$:  *Endergonic*. Product is disfavored

Oxidation of food: *Exergonic*.

Making new chemical bonds, mechanical work, maintenance of gradients: *Endergonic*.

Staying alive: Priceless.

Gibb's Free Energy and Equilibrium

What this means is that if all the big, complex molecules of life were sitting there, they would ultimately just fall apart...

$$\Delta G^{\circ} = -RT \ln(K_{eq})$$

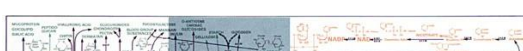
For example, the reaction $ATP \rightarrow ADP$ has a ΔG° of -30.5 kJ/mol. So, if I make up a batch of ATP and shake it around, after a **gazillion** years the equilibrium constant (ADP / ATP) will look like...

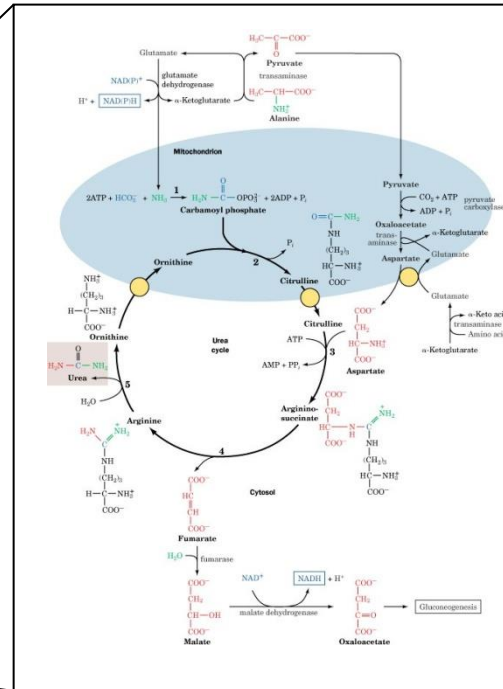
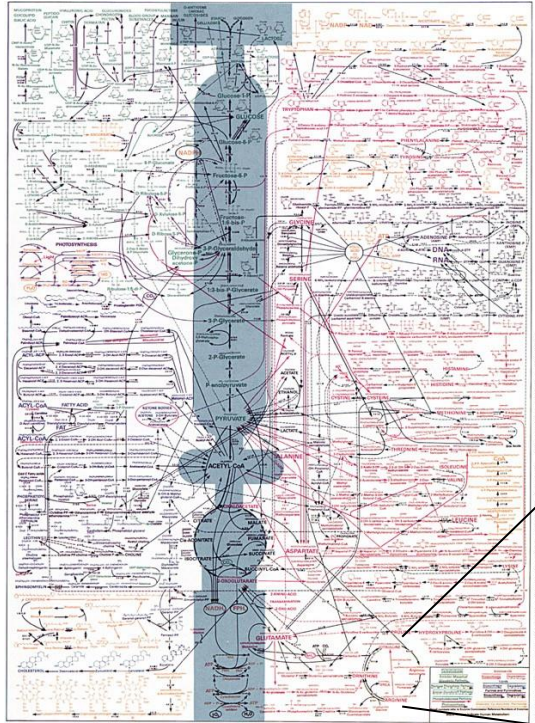
$$K_{eq} = \left(\frac{[ADP]}{[ATP]} \right) = e^{((30.5 \text{ kJ/mol}) / (.008314 \times 298))} = 2.2 \times 10^5$$

In other words, all but 1/220000th of the ATP has spontaneously decomposed to ADP. Since we need ATP for energy, that is bad.

We need a way to get around this problem...

A Solution to the Equilibrium Problem: Metabolic Pathways

- Metabolism is a network of chemical reactions which are almost always mediated by enzymes
 - A linked set of reactions within the network is a *metabolic pathway* or *cycle*.
- 
- A detailed metabolic map showing various pathways such as glycolysis, the TCA cycle, and amino acid metabolism. Enzymes are labeled with E1, E2, etc., and the map is color-coded to distinguish different metabolic regions.



- This allows for **'linked reactions'** where we sortof **'grab'** unfavorable products and put them through a **highly favorable reaction** before they can decompose...

Metabolic Pathways

- In sum, *pathways* are almost *always exergonic*, and very often largely so.

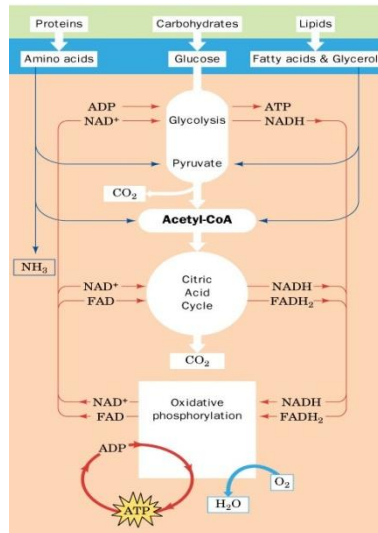
e.g. from Glucose to Pyruvate is ≈ -130 kcal/mol

- This does not mean that *all* reactions in the pathway are exergonic

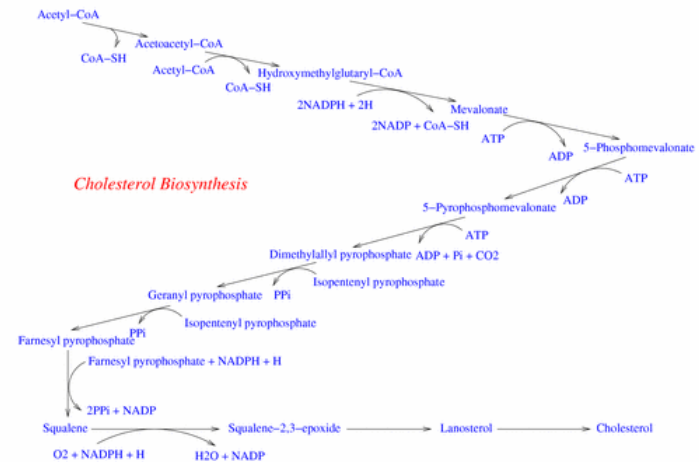
e.g. from Glucose to Glyceraldehyde-3-Phosphate is $\approx +20$ kcal/mol

- Metabolic pathways can be *Catabolic* (break stuff down - degradation) or *Anabolic* (build stuff up - synthesis)

- *Catabolic* pathways start from a range of molecules (carbohydrates, proteins, lipids), converging on a relatively small number of intermediates.



- *Anabolic* pathways start from a small number of molecules (*i.e.* pyruvate, Acetyl CoA, citrate) and make a huge variety of products



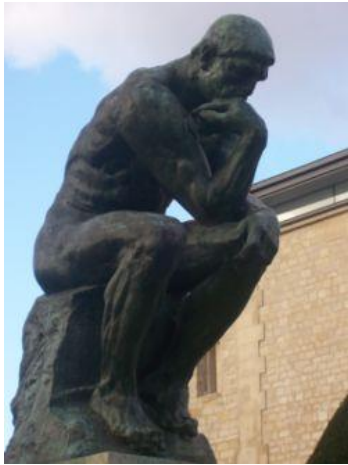
Regulating Metabolic Pathways

- Control of metabolic pathways is by *regulating the expression or activity* of enzymes that catalyze 'committed steps'
 - Regulation of enzyme activity = FAST
 - Regulation of expression = SLOW
- Metabolic processes are *compartmentalized* in every organism higher than a Eukaryote

Organelle	Function
Mitochondrion	Citric acid cycle, electron transport and oxidative phosphorylation, fatty acid oxidation, amino acid breakdown
Cytosol	Glycolysis, pentose phosphate pathway, fatty acid biosynthesis, many reactions of gluconeogenesis
Lysosomes	Enzymatic digestion of cell components and ingested matter
Nucleus	DNA replication and transcription, RNA processing
Golgi apparatus	Posttranslational processing of membrane and secretory proteins; formation of plasma membrane and secretory vesicles
Rough endoplasmic reticulum	Synthesis of membrane-bound and secretory proteins
Smooth endoplasmic reticulum	Lipid and steroid biosynthesis
Peroxisomes (glyoxisomes in plants)	Oxidative reactions catalyzed by amino acid oxidases and catalase; glyoxylate cycle reactions in plants

Course Outline

Who started thinking about metabolism first?



Paris



Washington



Kyoto

Metabolic Research: The 'Pee' Years

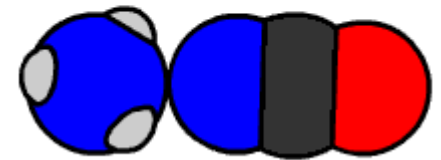
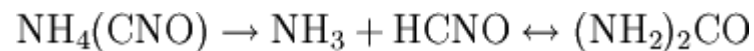


Friedrich Wöhler

Scientists in the early 1800's were aware that differences existed between the chemical reactions of life and plain old boring chemical reactions

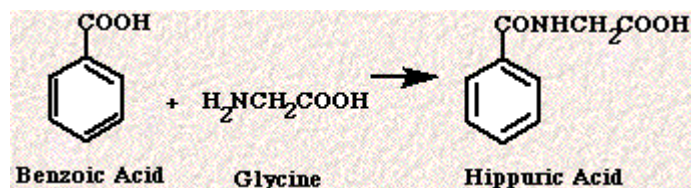
Their explanation for this difference?: The '*vital force*' a.k.a the '*internal flame*'

The *Science* of metabolism really started when Wöhler (accidentally) synthesized Urea from Ammonium Cyanate



Many of Wöhler's experiments were carried out on himself or, if that was too dangerous – his dog!

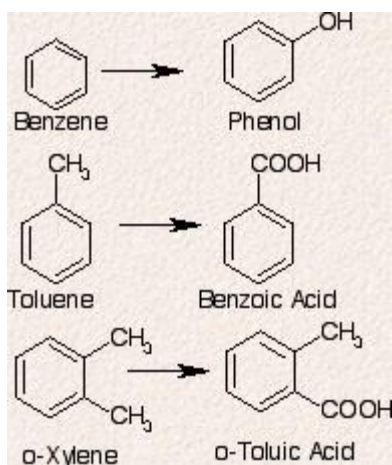
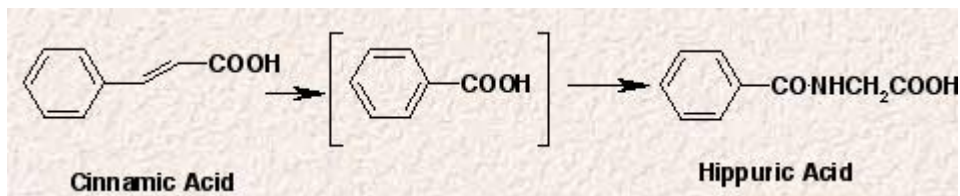
1841 – First productive human metabolism experiment: *Alexander Ure* observes conversion of Benzoic Acid to hippuric acid and proposes Benzoic Acid as a treatment for Gout



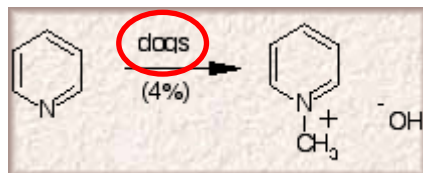
More on Understanding Pee

The first strategy of metabolic chemists: 'Feed 'em some phenyl derivative and we'll see what comes out in the urine'. Mid to late 1800's.

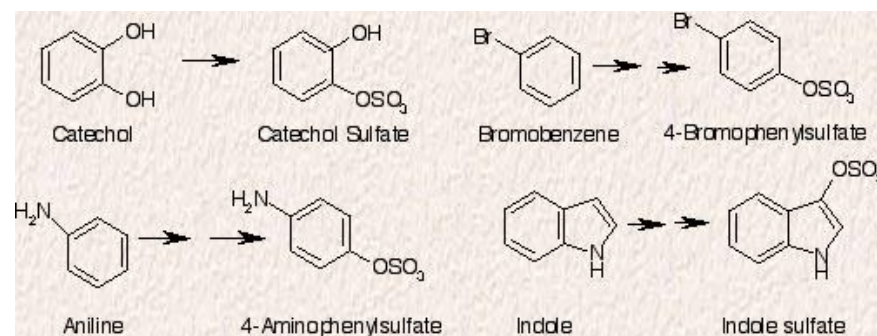
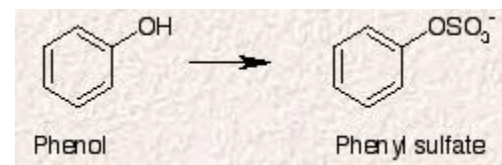
Oxidation



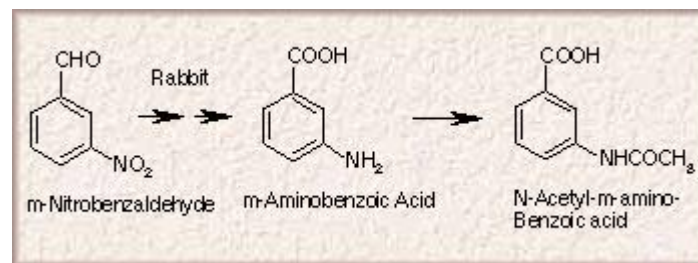
Methylation



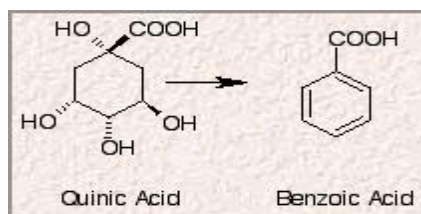
Sulfate Conjugation



Acetylation

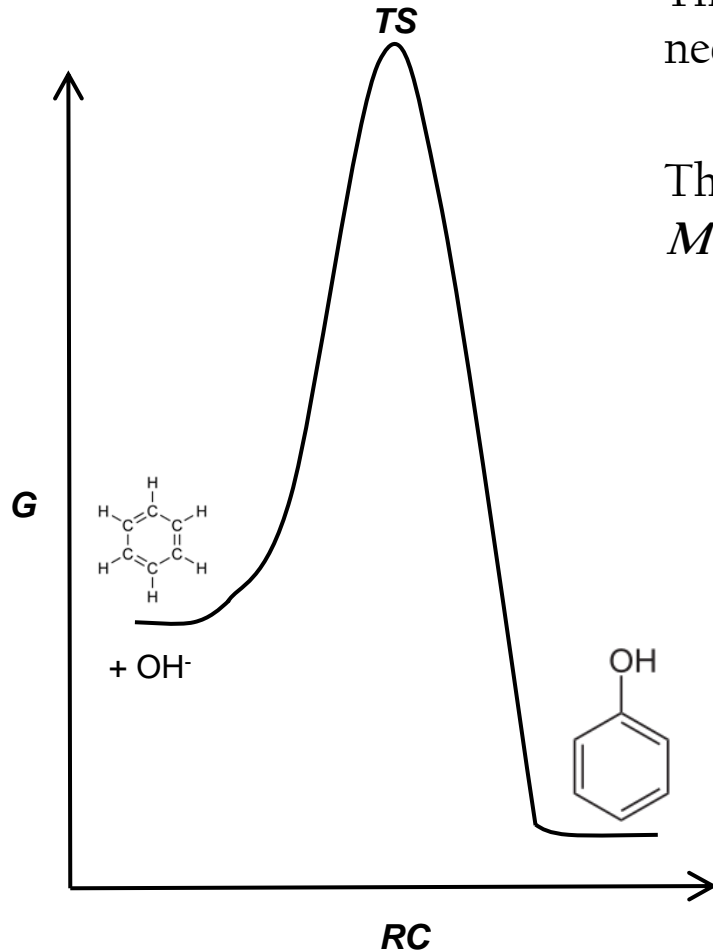


Reduction



Most of these chemistries are very hard. The products are *very stable*, but if you throw in the reactants *nothing happens*... Hunh?

The Trouble With Making Pee:



The reaction is favorable, but it'll never happen. We need Catalysts!

This is the basis for the connection between *Metabolism* and *Enzymes*.

Note that in this case, even **unstable products** will hang around for quite a while once they are formed, so there's no need to 'grab' them quickly. This is called '**kinetic trapping**' and it's in large part why we are able to hang on to **ATP** once we've made it...

Same Bat-time, Different Bat-channel

Fortunately, at the same time as our metabolic chemists were busy examining pee, Eduard Buchner was hard at *killing yeast*.

Interestingly, he found that *yeast extract* could *still ferment sugar*!



1907



This was actually about *40 years after* Payen and Persoz first isolated an enzyme (1833) that could break down starch. We now know and love this enzyme as *amylase*

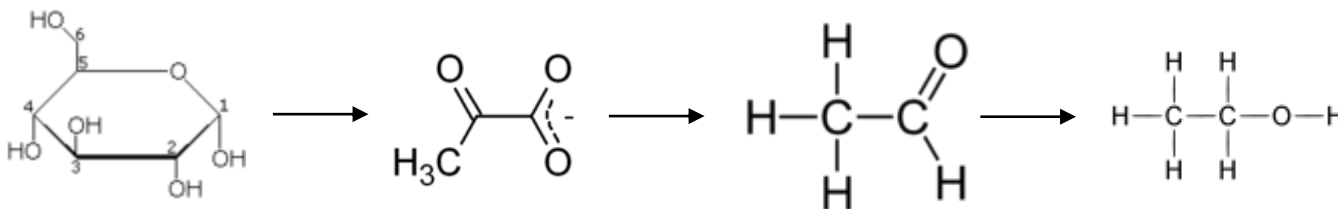
The difference was that Buchner knew he was dealing with proteins, mainly because of the work of this man:

Egg albumin:

Carbon	400	30,574.80	54.90
Hydrogen	620	3,868.68	6.95
Nitrogen	100	8,851.80	15.89
Oxygen	120	12,000.00	21.55
Phosphorus	1	196.16	0.35
Sulphur	1	<u>201.17</u>	<u>0.36</u>
		55,692.61	100.00



Gerardus Mulder
1802-1880

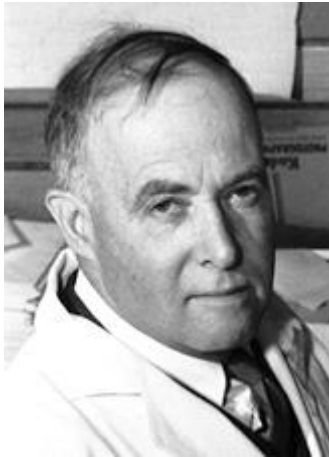


What Are These Things Called Enzymes?

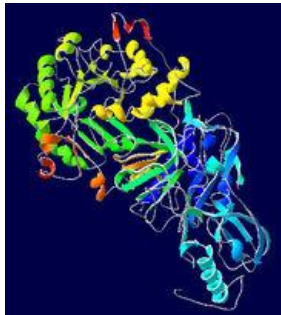
OK, so something non-living and associated with proteins in Yeast ferments sugar.
But what is this thing?

The protein itself? Surely not!

Then, along comes this guy:



James B. Sumner
1887-1955



He starts trying to isolate an enzyme in its pure form

In 1926 he gets crystals of Urease

He is then generally ignored for the next 10 years or so

In 1929, Northrop and Stanley do the same with *Pepsin* and now people start to believe (slowly)



1946

<http://nobelprize.org/>



John H.
Northrop



Wendell M.
Stanley

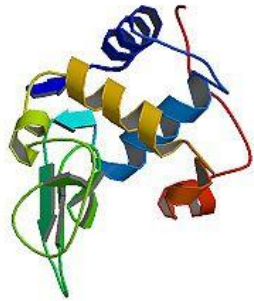
Pioneers of Enzyme Function



Lord David Chilton
Phillips (1924 –
1999)

Got X-ray crystal structure for Lysozyme in 1965

The beginning of *Structural Biology*



We now know the structure of lysozyme down to 1.04 Å
(1.04×10^{-10} m, C-H bond ~ 1.1 Å).



Leonor Michaelis
1875–1949



Maud Menten
1879–1960

Pioneered enzyme kinetics



"I think that enzymes are molecules that are complementary in structure to the activated complexes of the reactions that they catalyse, that is, to the molecular configuration that is intermediate between the reacting substances and the products of reaction for these catalysed processes. The attraction of the enzyme molecule for the activated complex would thus lead to a decrease in its energy, and hence to a decrease in the energy of activation of the reaction, and to an increase in the rate of the reaction"
- 1948



Chemistry
(1954)

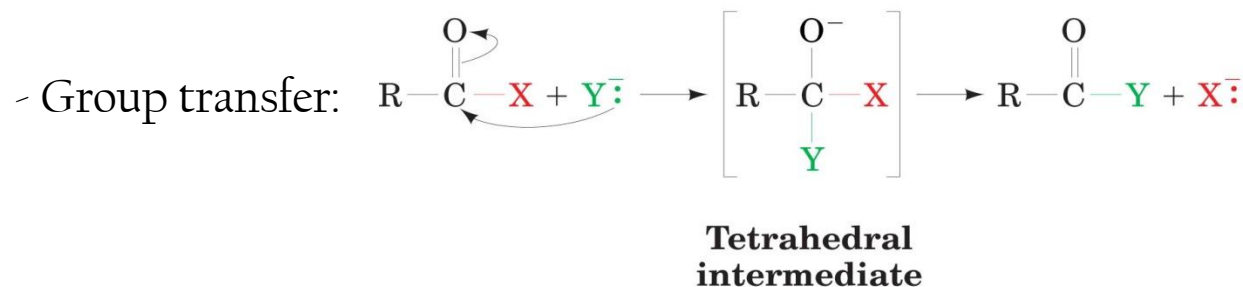


Peace (1962)

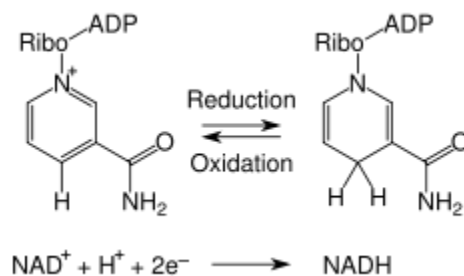
Metabolism Overview – Organic Chemistry

- All metabolic chemistry falls under one of the following 4 categories:

1. Group transfer
2. Oxidations and Reductions
3. Elimination / Isomerization
4. Carbon bond making/breaking

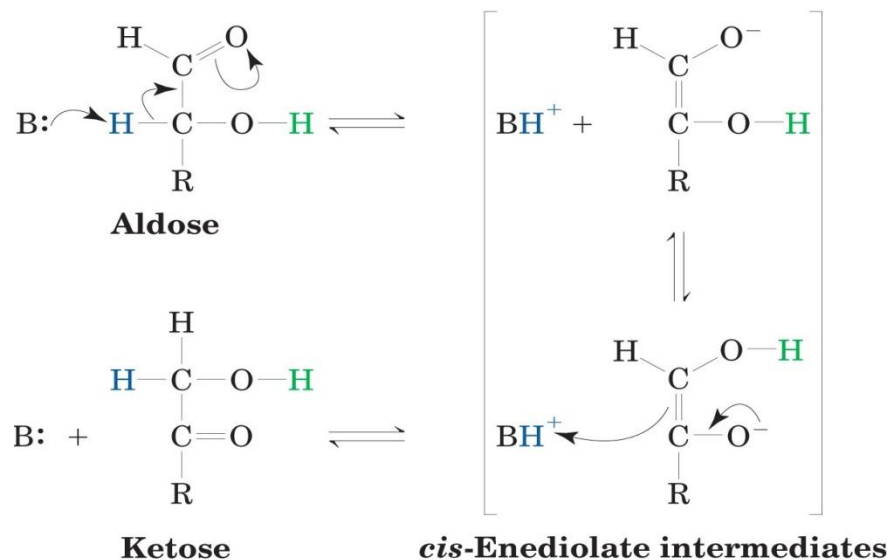


- Oxidation/reduction:



More Organic Chemistry

- Elimination / Isomerization:



- Carbon bond making/breaking:

(c) **Decarboxylation of a β -keto acid**

