Chemistry of Medicine I (by Mori)

医用化学第一（森　担当分　4回）

Content:

0. Evolutionary Medicine 進化医学
1. Diabetic mellitus 糖尿病
2. Atherosclerosis 動脈硬化
3. Alzheimer’s disease アルツハイマー病

- Download the handout from Katayama lab HP

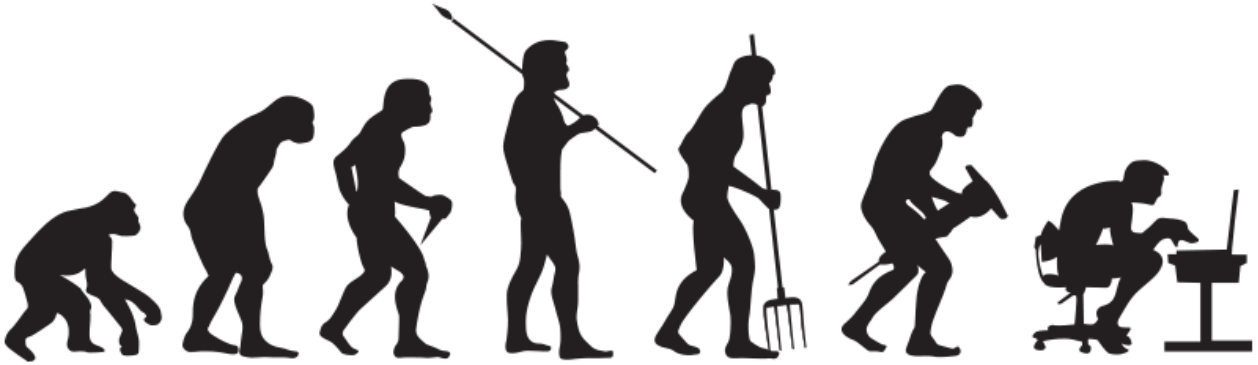
  リンク⇒講義資料

- Submit mini-test via e-mail to me.

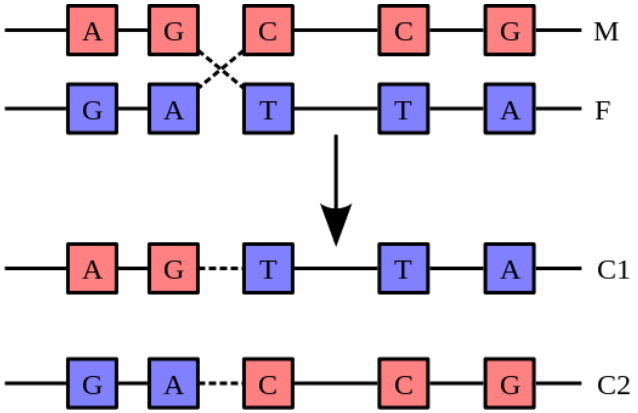
  mori.takeshi.880@m.kyushu-u.ac.jp

  subject: mini-test

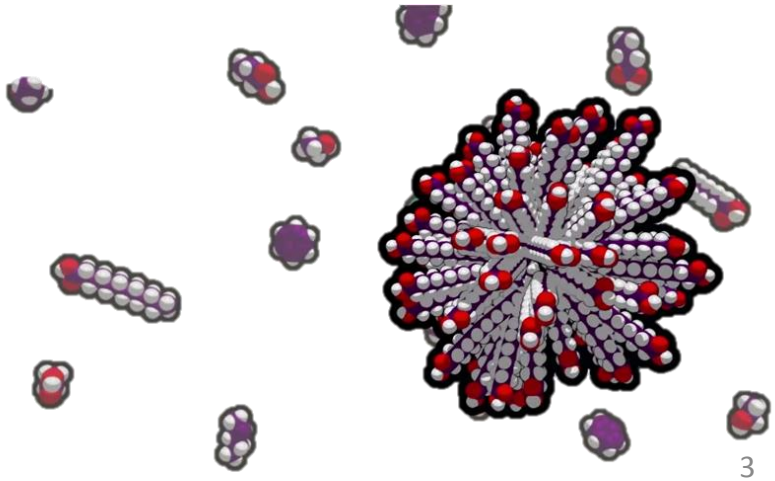
Evolutionary medicine
進化医学



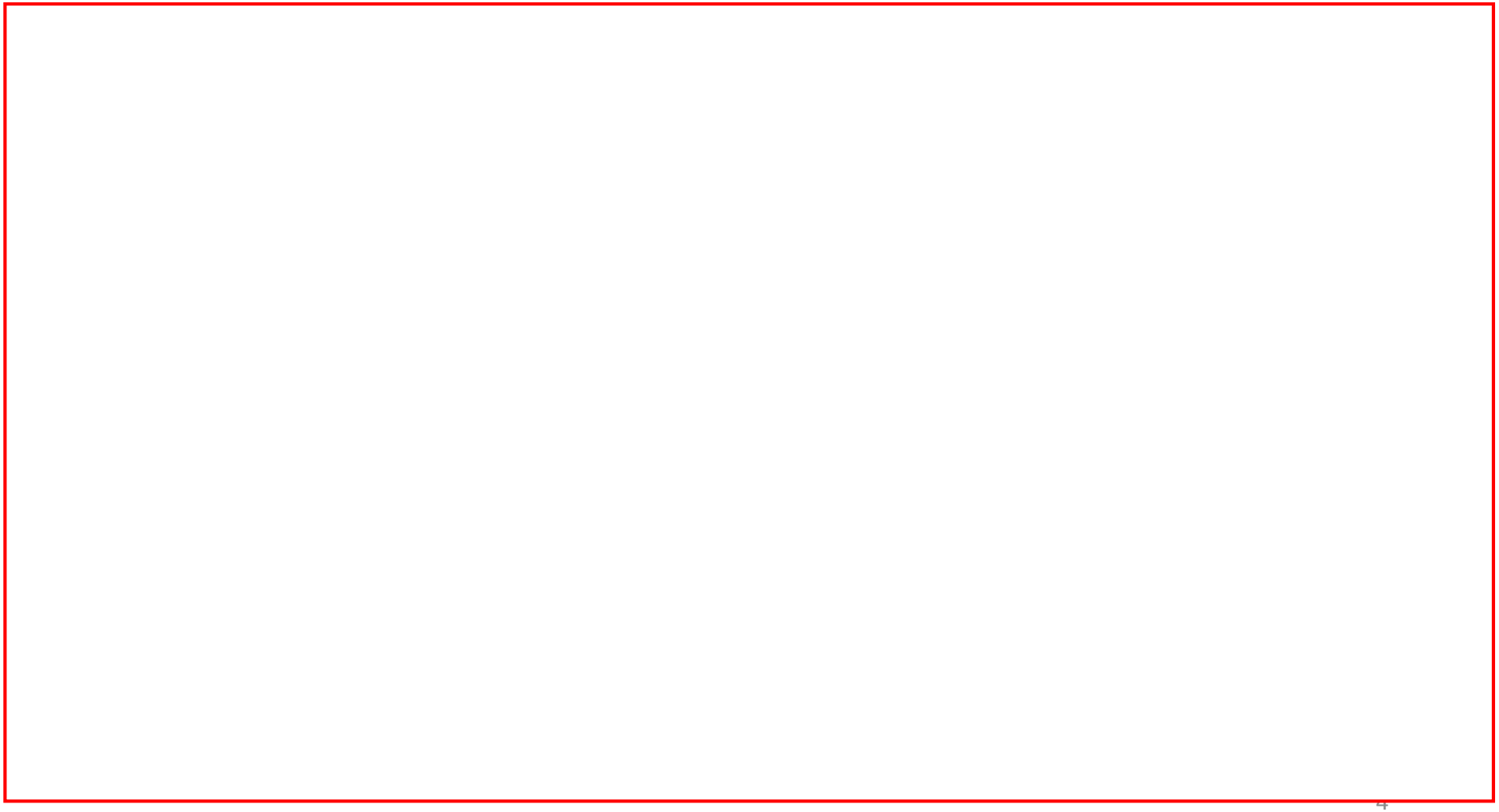
Molecular evolution
分子進化



Chemical evolution
化学進化



Why we'd better think based on evolution?
なぜ進化で考えると良いのか？



0. Darwinian medicine (evolutionary medicine)
ダーウイン医学（進化医学）

- How people get sick => Why people get sick
- Why evolution has shaped these mechanisms in ways that may leave us susceptible to disease.
- It works well to explain diseases including cancer, infection, autoimmunity, anatomy, mental illness (がん、感染症、自己免疫疾患、解剖学、精神疾患）

1962
James Neel

How to make question based on Darwinian medicine

Q1: Why scurvy occurs?

壊血病という病気はなぜ起こるのか？

A1: Lack of vitamin C causes scurvy

Vitamin Cが欠乏すると壊血病になる。

Q2: Why lack of vitamin C causes scurvy?

vitamin Cが欠乏するとなぜ壊血病になるのか？

A2: vitamin C is needed for blood coagulation.

血液凝固にvitamin Cが必要だから

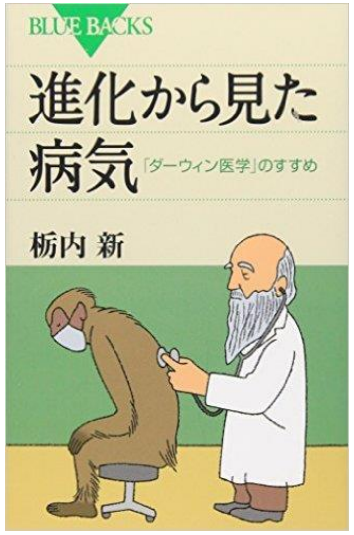
Q3: Why human does not biosynthesize important vitamin C? (Darwinian)

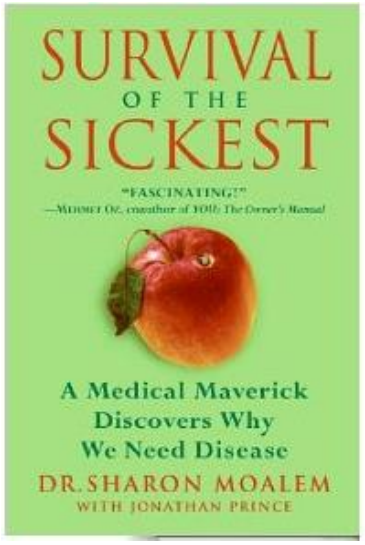
なぜ大事なvitamin Cを生合成しないのか？

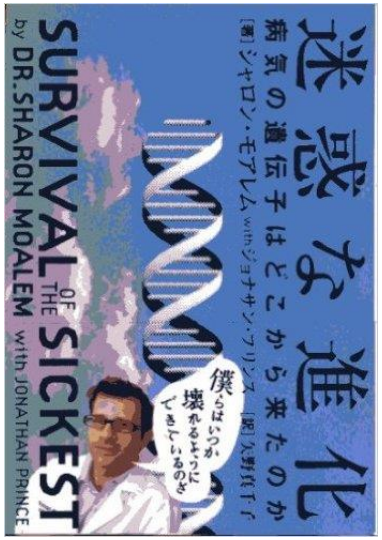
A3: Up to rodent synthesize vitamin C. Change in metabolism and food.

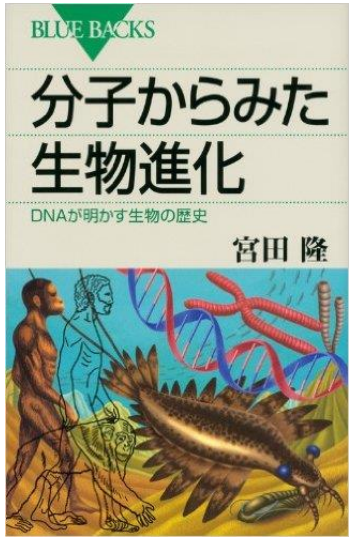
げっ歯類までは生合成する。代謝系における変化。食物の変化。

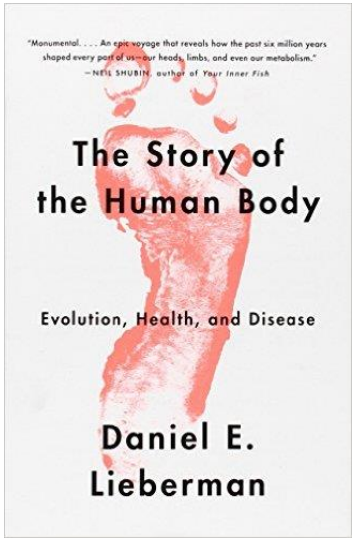
References

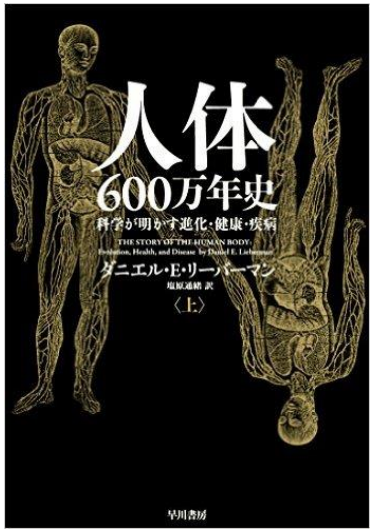

BLUE BACKS
進化から見た病気
「ダーウィン医学」のすすめ
栃内 新


SURVIVAL OF THE SICKEST
"FASCINATING!"
A Medical Maverick Discovers Why We Need Disease
DR. SHARON MOALEM
WITH JONATHAN PRINCE

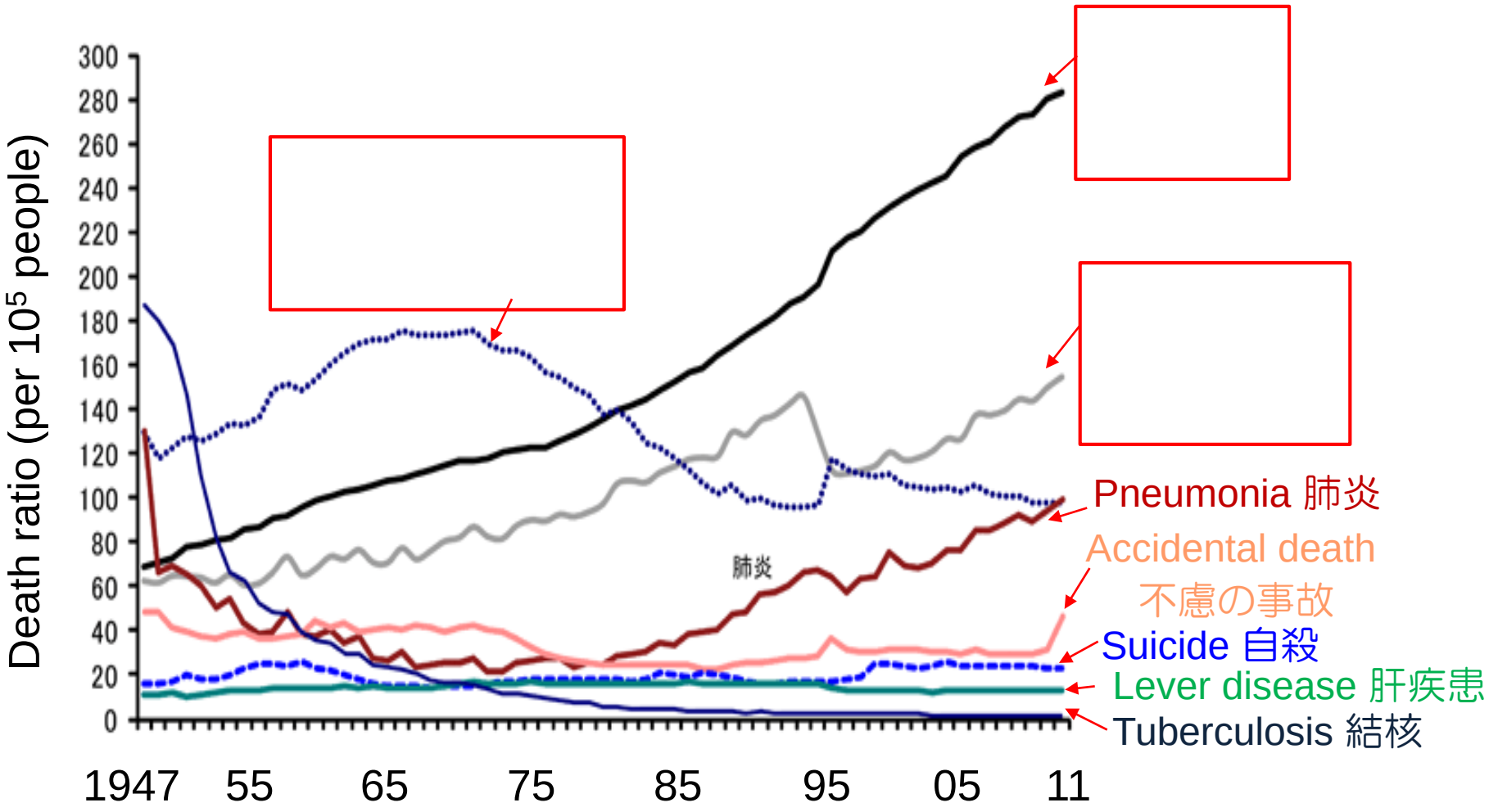

迷惑な進化
病気の遺伝子はどこから来たのか
SURVIVAL OF THE SICKEST
by DR. SHARON MOALEM with JONATHAN PRINCE


BLUE BACKS
分子からみた生物進化
DNAが明かす生物の歴史
宮田 隆


"Monumental. . . . An epic voyage that reveals how the past six million years shaped every part of us—our heads, limbs, and even our metabolism."
—NEIL SHUBIN, author of Your Inner Fish
The Story of the Human Body
Evolution, Health, and Disease
Daniel E. Lieberman


人体
600万年史
科学が明かす進化・健康・疾病
THE STORY OF THE HUMAN BODY
ダニエル・E・リーバーマン
〈上〉
早川書房

Cause of death in Japan



Natural selection (Darwin, 1858)

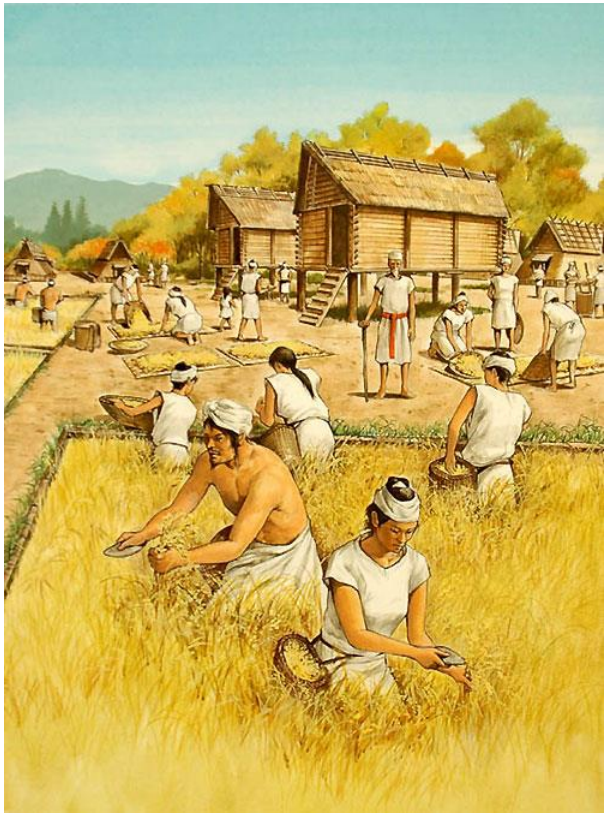
The giraffe ancestor who has longer neck (the fittest) survived, and then long necks became common in population.

Change in life style

200k years ago
(hunting, sampling)

Much exercise
Efficient energy absorption
Miscellaneous food
Small group

10k years ago
(farming)



grain (carbohydrate)
Livestock (milk)

present

satisfaction (fat, carbohydrate, salt), lack of exercise
work at midnight
longevity, stressful, hygiene, reading

Mismatch diseases

Acid reflux　胃酸の逆流	Flat foot 偏平足
Acne　にきび	Gout 痛風
Alzheimer's disease アルツハイマー病	Hemorrhoid 痔
Apnea 無呼吸	Hypertension 高血圧
Asthma 喘息	Insomnia 不眠症
Athlete’s foot 水虫	Irritable bowel syndrome 過敏性腸症候群
Cancer がん	Lactose intolerance 乳糖不耐性
Carious tooth 虫歯	Low back pain 腰痛
Cirrhosis of the liver 肝硬変	Metabolic syndrome メタボリックシンドローム
Constipation 便秘	Multiple sclerosis 多発性硬化症
Coronary heart disease 冠状動脈性心疾患	Myopia 近視
Crohn’s disease クローン病	Osteoporosis 骨粗しょう症
Depression うつ病	Scurvy 壊血病
Diabetes type 2 二型糖尿病	

Ref: “The story of the human body”

Person who overcomes mismatch diseases will appear by genetic mutation. Is this genotype spread in homo sapience?

今後、Mismatch diseasesを進化で克服した個人が出てきたとして、その子孫がやがて人類のマジョリティーを占めるようになるか？

1. Diabetic mellitus (DM) 糖尿病

1. What is DM 糖尿病とは
2. Glycation causes diabetic complications 合併症の原因は糖
3. Why human chose glucose?　なぜ、それでもヒトはglucose を選んだのか？
4. Mechanism to control BGL 血糖値の調節機構
5. Cause of DM 糖尿病の原因
6. Therapy of DM 糖尿病の治療

1.1 What is DM 糖尿病とは

Which one does include more glucose?

Total amount of blood 5L

Coke 350 mL

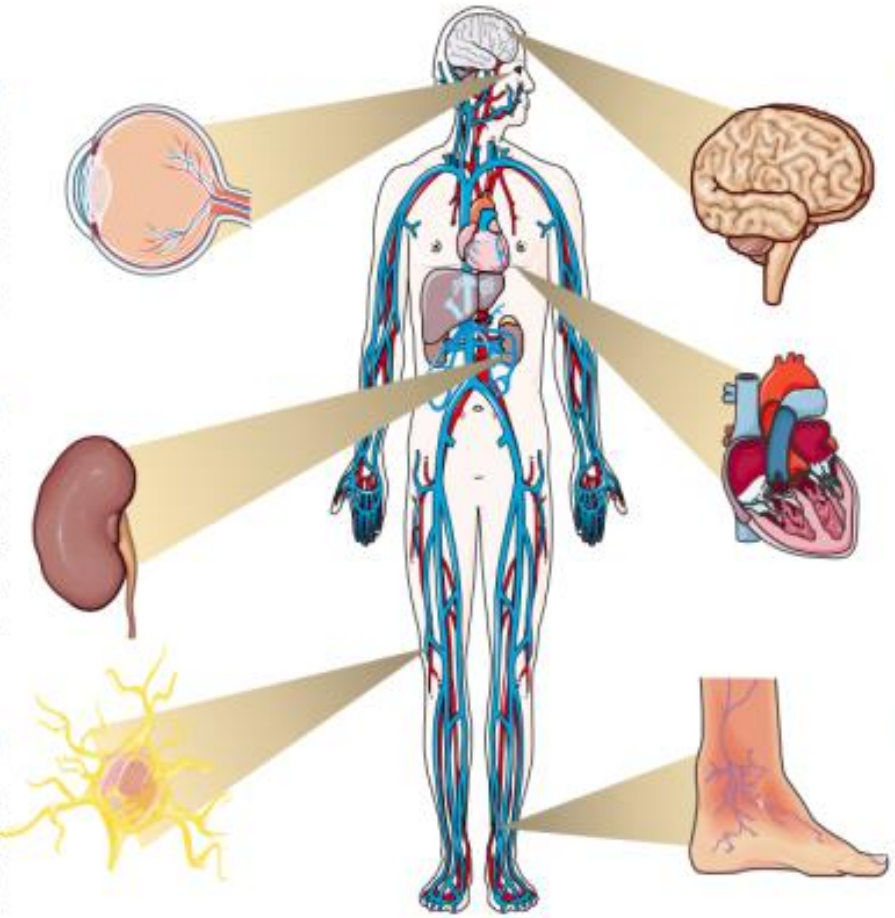
Diabetic complications 糖尿病合併症

Microvascular

Eye
High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney
High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy
Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.



Macrovascular

Brain
Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart
High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities
Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

How dose high BGL cause these diseases?

Diabetes mellitus

- High glucose conc. in blood. (≥ 126 mg/dL, HbA1c ≥ 6.5%)
- Type I: destruction of pancreatic β cell, leading to depletion of insulin. Then become high glucose conc. 膵臓β細胞が破壊され、インシュリンが枯渇し、その結果、高血糖になる。
- Type II: decrease in secretion of and response to insulin. 90% of diabetes patients.
- 5% of the world's adult population. 7.4 million in Japan.
- Causing diabetic complications （合併症）：

  diabetic neuropathy 糖尿病性神経障害
  diabetic retinopathy 糖尿病性網膜症
  diabetic nephropathy 糖尿病性腎症

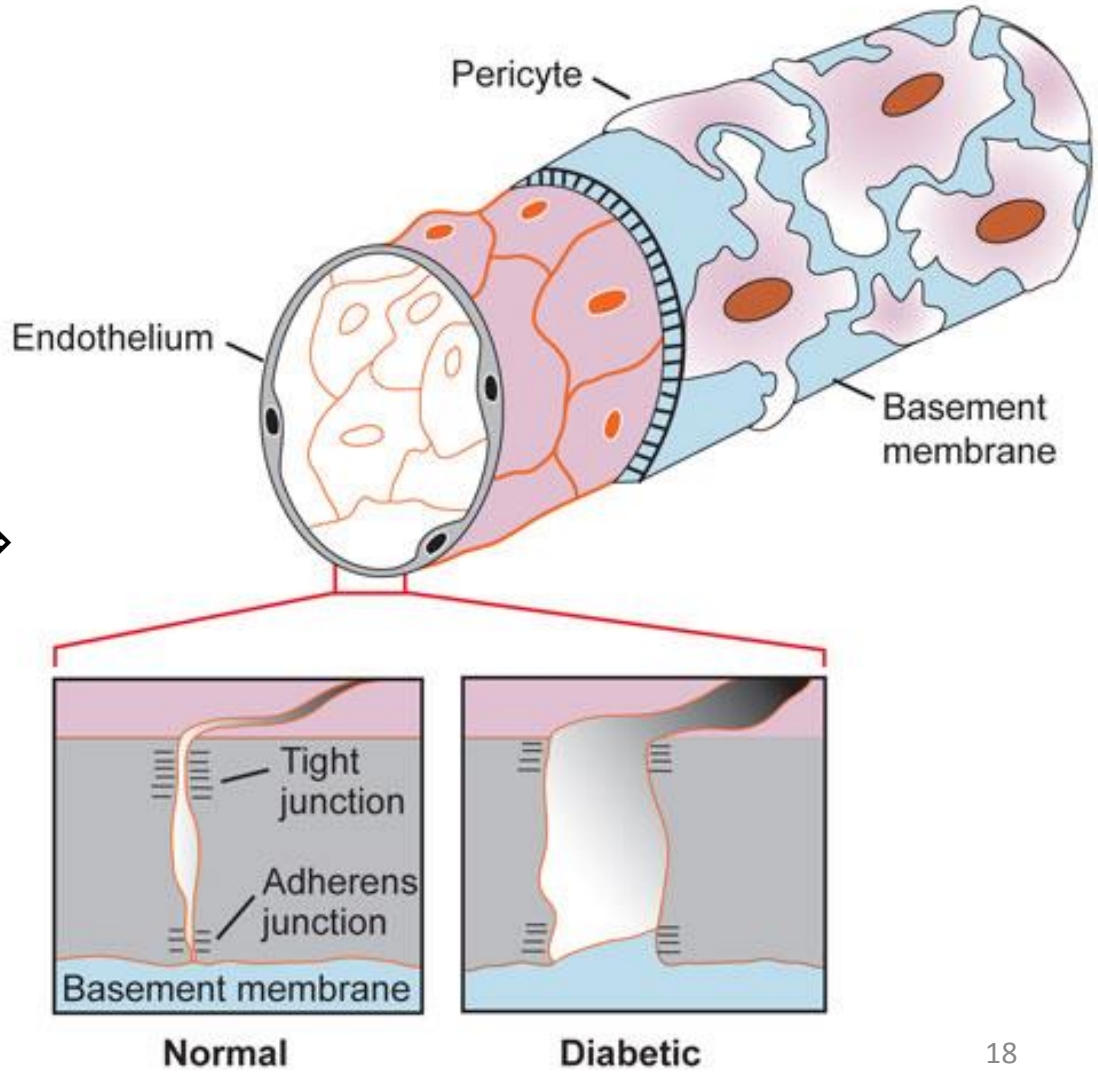
  → Microvascular disease 微小血管障害

  myocardial infarction 心筋梗塞
  peripheral vascular disease 末梢血管障害

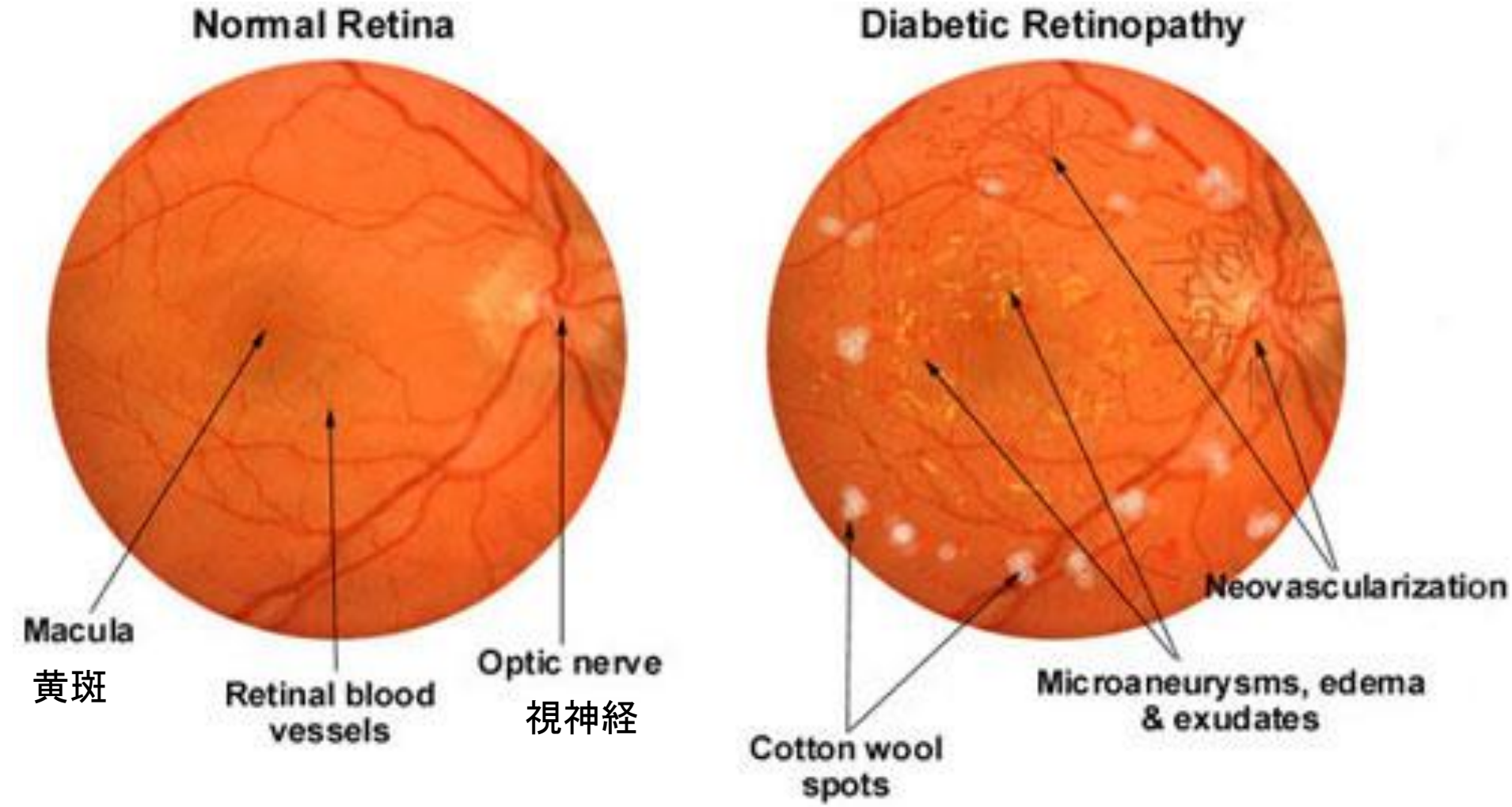
  → Macrovascular disease 大血管障害

Mechanism of diabetic retinopathy

1. Endothelial cell (血管內皮細胞) and basement membrane (基底膜) exposed to high blood glucose conc.
2. Glycation of endothelial membrane protein and basement membrane protein.
3. Thickening and weakening of basement membrane.
4. Loss of pericyte (周皮細胞)
5. Leakage of plasma ⇒ Retinal edema （浮腫）、exudate （滲出）
6. microaneurysm（微小動脈瘤）⇒ hemorrhage（出血）



Diabetic retinopathy 糖尿病性網膜症

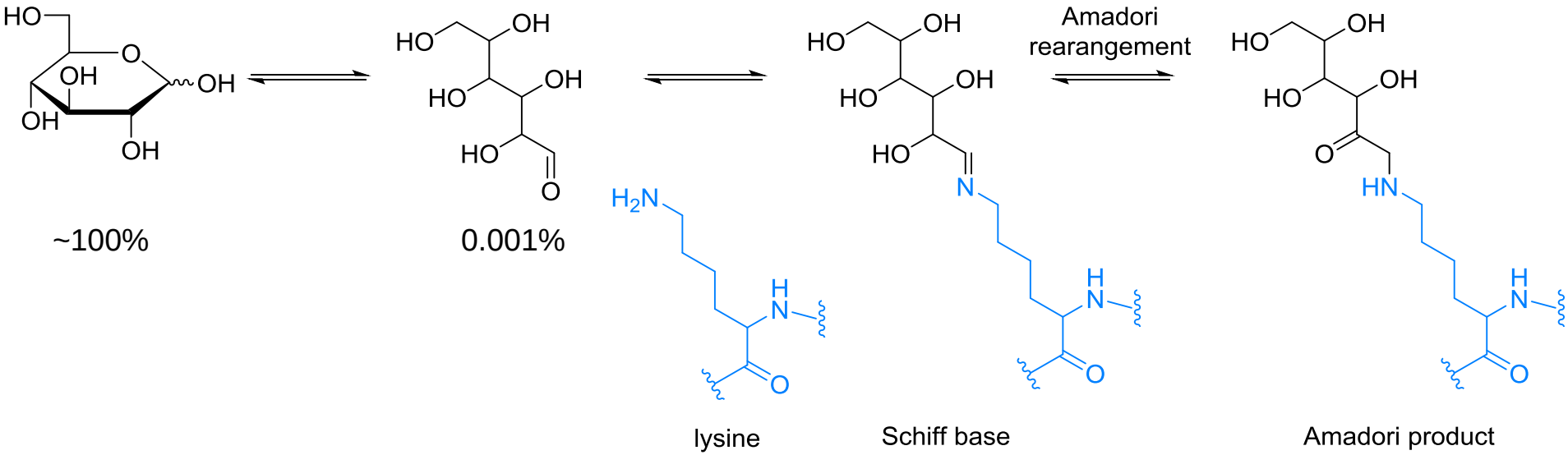


1.2 Glycation causes diabetic complications

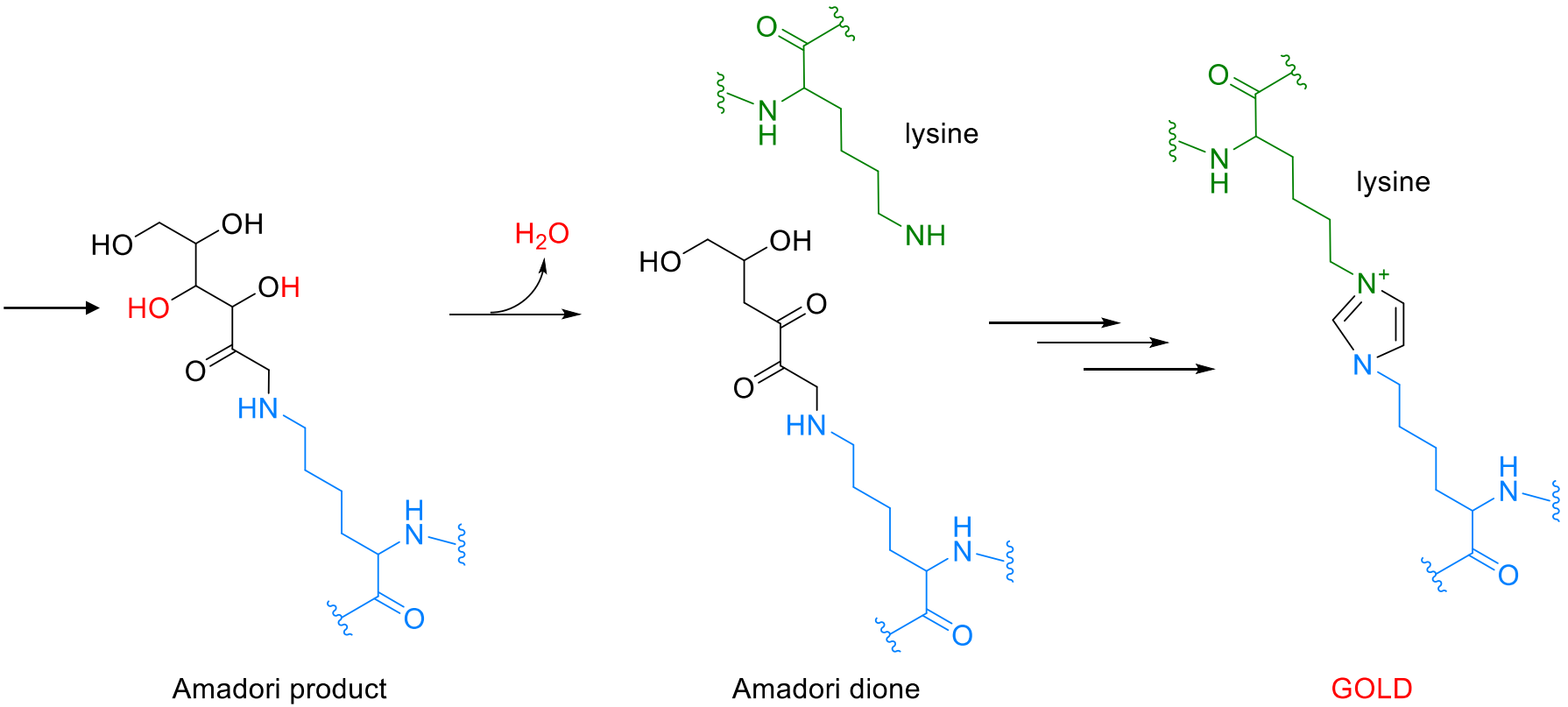
合併症の原因は糖化

AGE (advanced glycation end product) 終末糖化産物

- Obtained by glycation of protein (Mailard reaction)
- Inducing protein denaturation leading to diabetic complications



AGE (advanced glycation end product)　終末糖化産物



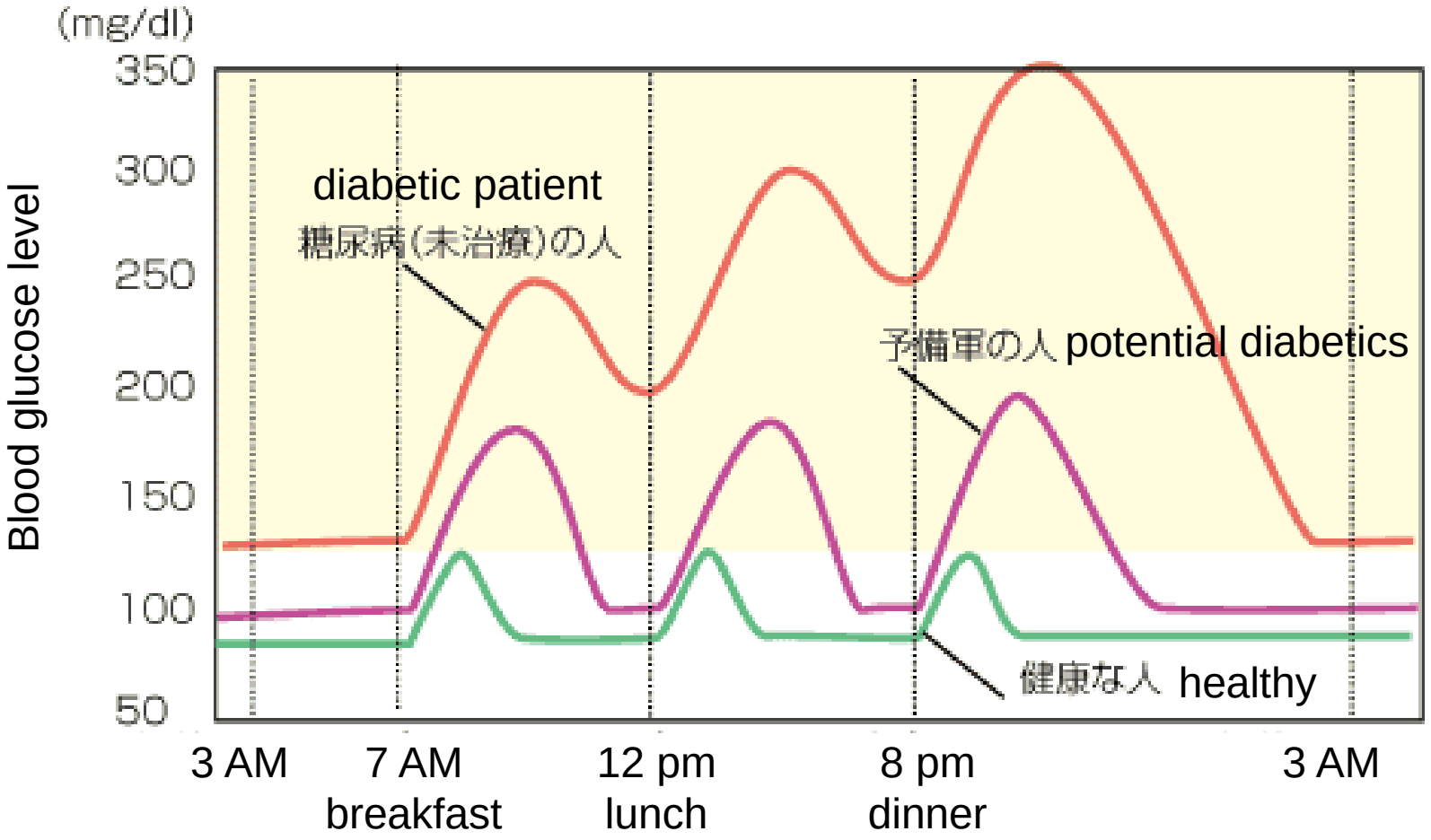
weeks, months, years (Mailard reaction)

Mailard reaction product tastes “Koku” コク

- Mailard reaction product itself is not tasty (bitter).
- But mixed with other taste, make the taste deeper one because of the simultaneous stimulation of different taste receptors.

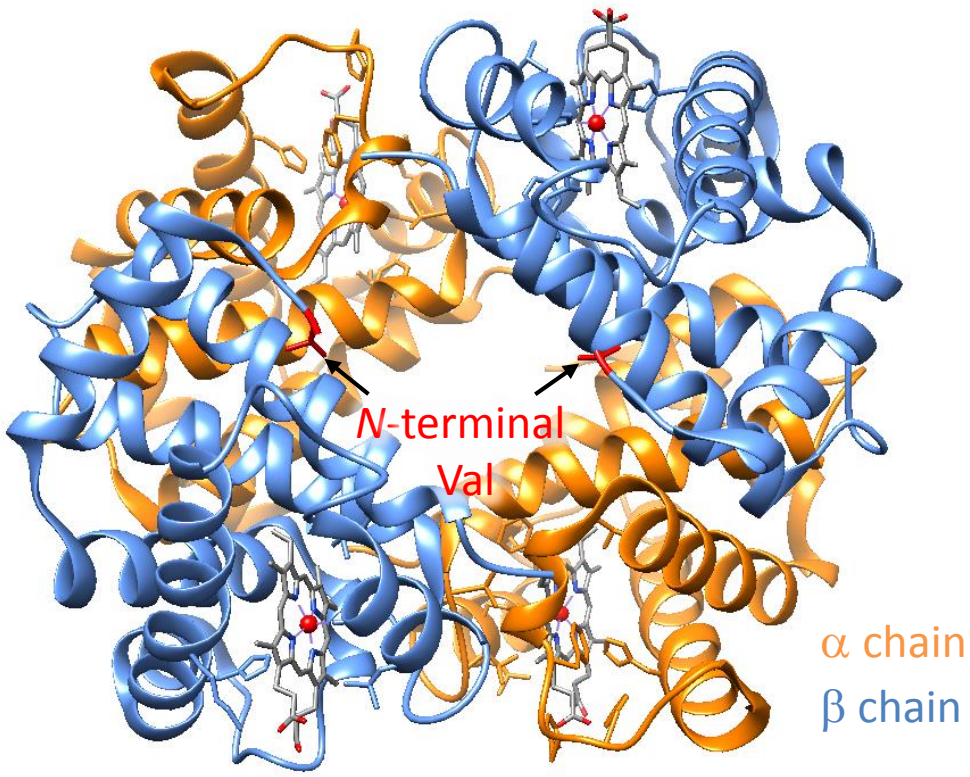
BGL is not constant

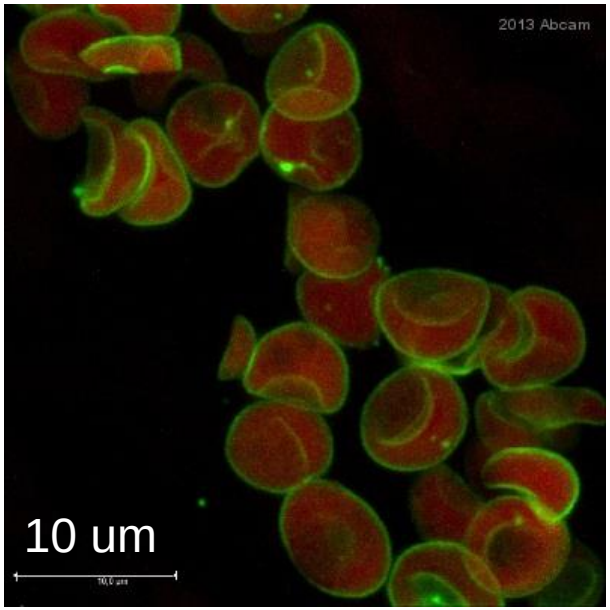
Affected by meal taking and daily stress. How can we remove such short-term effects?



Monitoring BGL by using hemoglobin (Hb)

- Half-life of red blood cell (RBC) is 2 months.
- Easy to sample enough amount of Hbs (90wt% of RBC in dry weight).
- Blood glucose conc. of more than a months can be monitored by checking Hb's glycation incorporated in RBC.
- HbA1c (one of β chains' N-terminus is glycated) is used. Content of HbA1c is analyzed by liquid chromatography.
- Diabetes: HbA1c ≥ 6.5%





Green: RBC's GLUT1

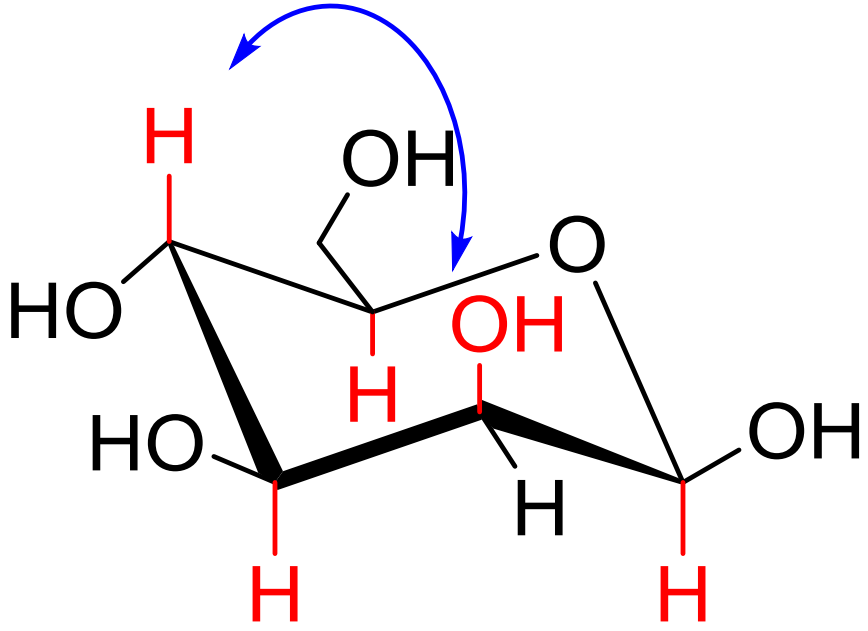
1.3 Why human chose glucose?

なぜ、それでもヒトはglucoseを選んだのか？

Why do we choose troublesome glucose as energy source?

なぜ厄介なグルコースを栄養に選んだのか？

There's no repulsion in glucose
グルコースは安定



D-glucose

D-mannose

Combustion energy of glucose is converted to ATP's chemical energy

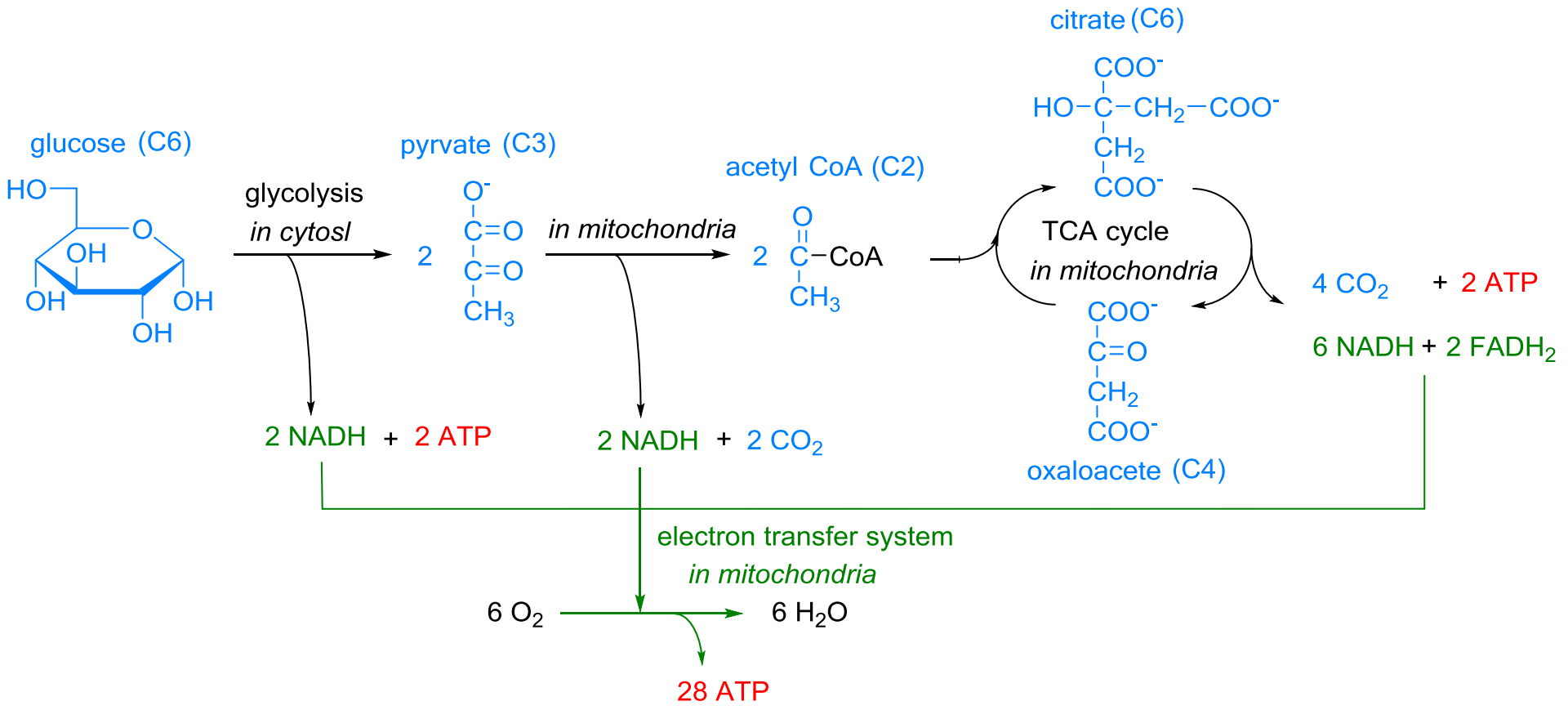
combustion

$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ H_2O + 6\ CO_2$ - 686 kcal/mol

respiration (combustion in body)

$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ H_2O + 6\ CO_2 + 32\ ATP$

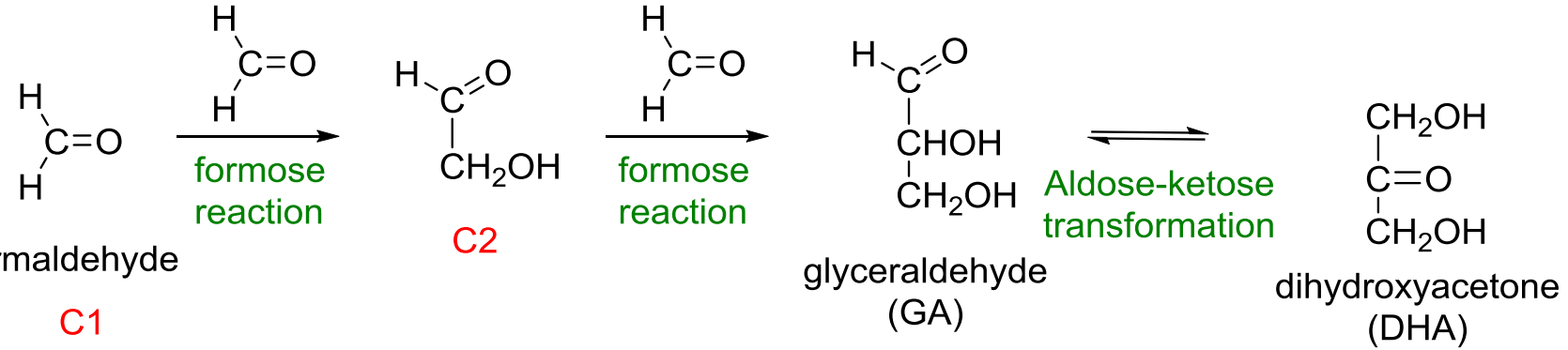
32 x - 7.3 = - 233 kcal/mol



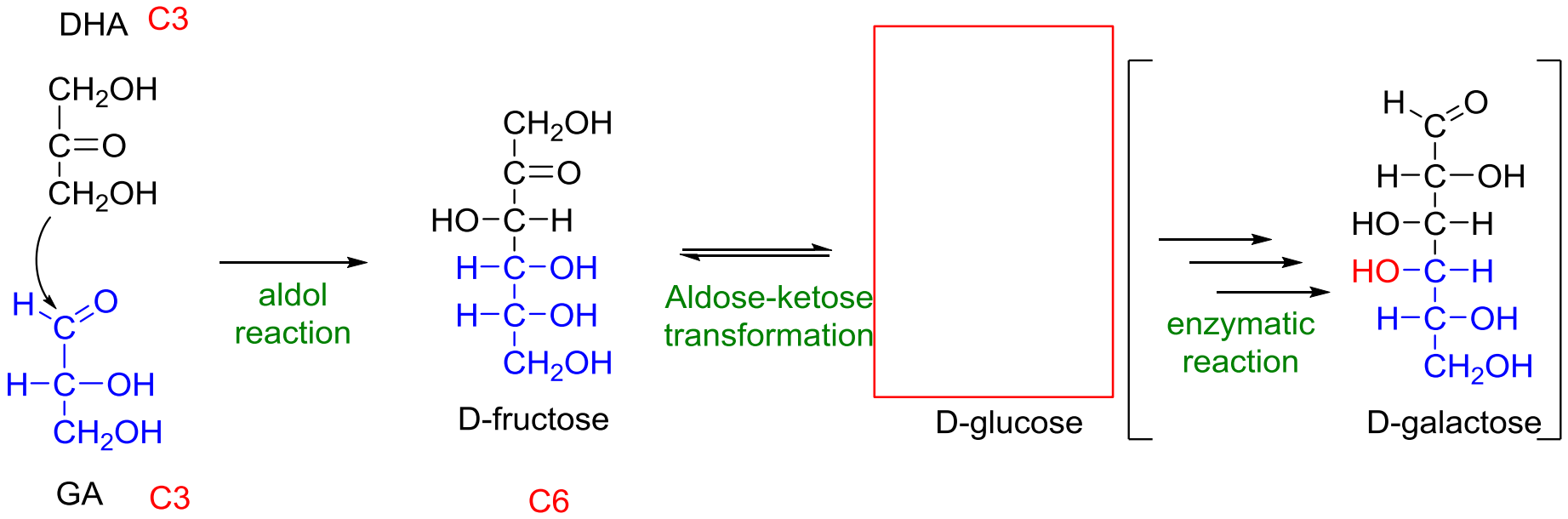
Prebiotic synthesis of glucose
生命によらない糖合成

2001 Viva Origino 119.

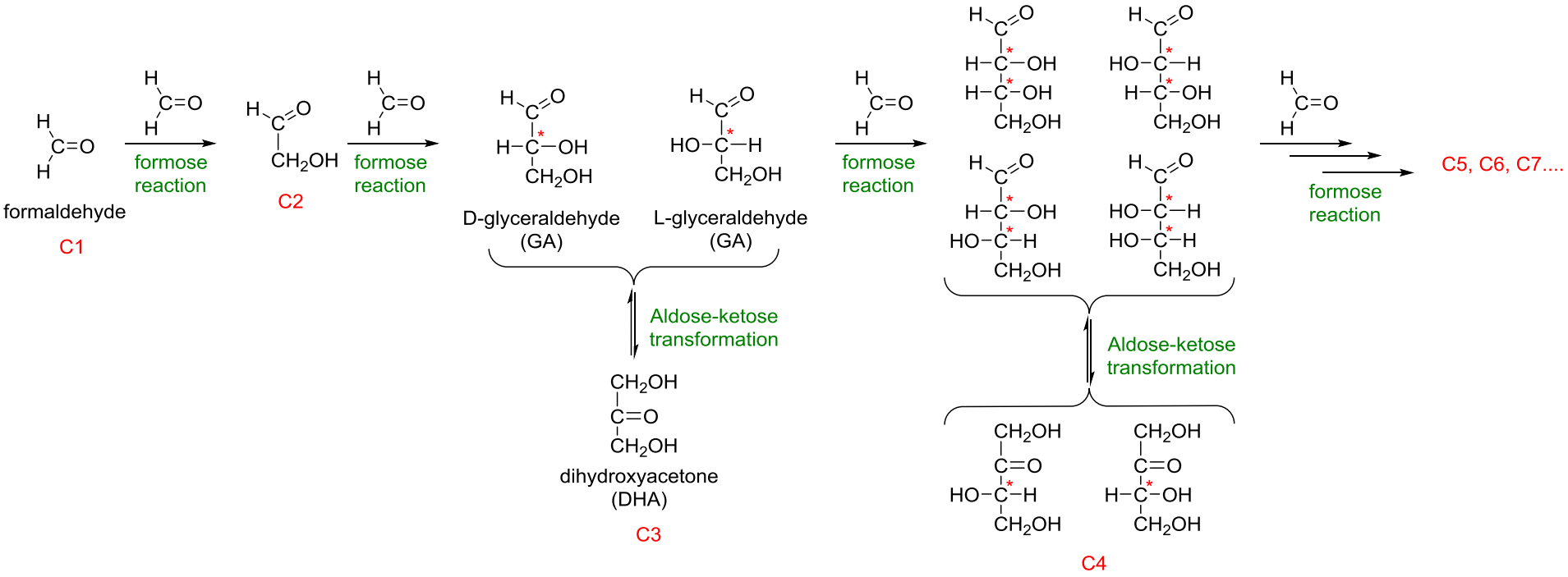
step 1



step 2

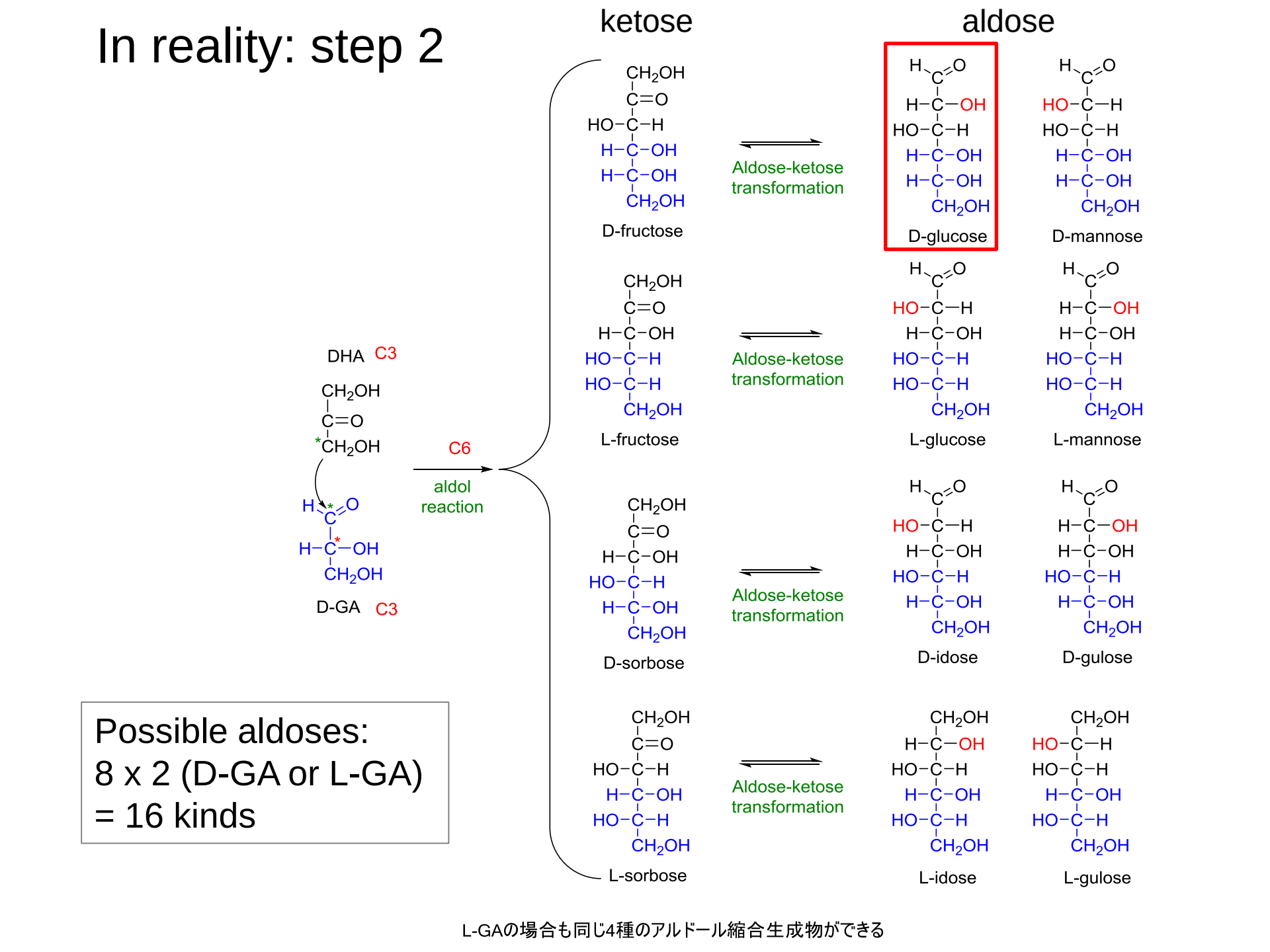


In reality: step 1



- C3 compounds was enriched.
- D-GA was selected.

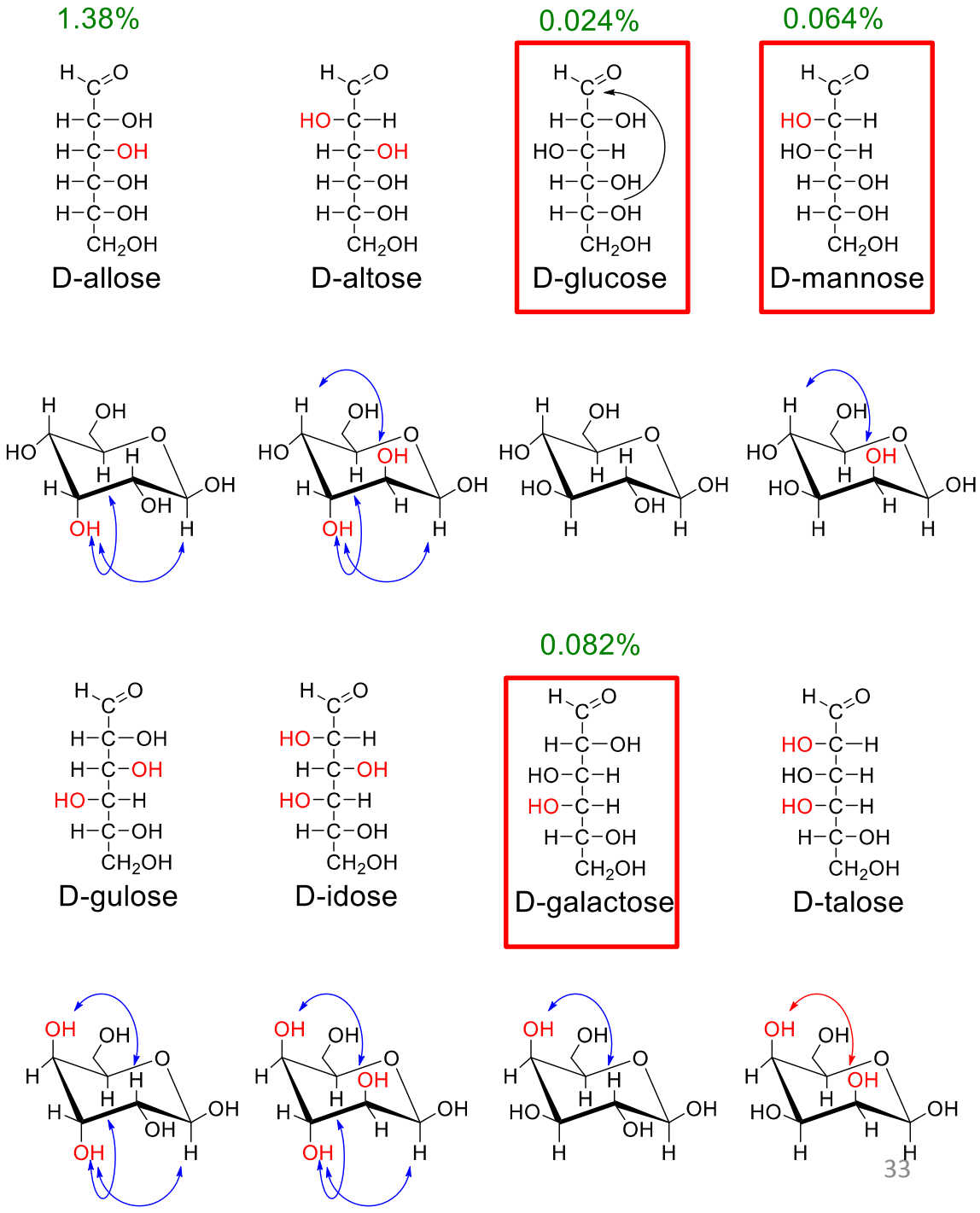
In reality: step 2



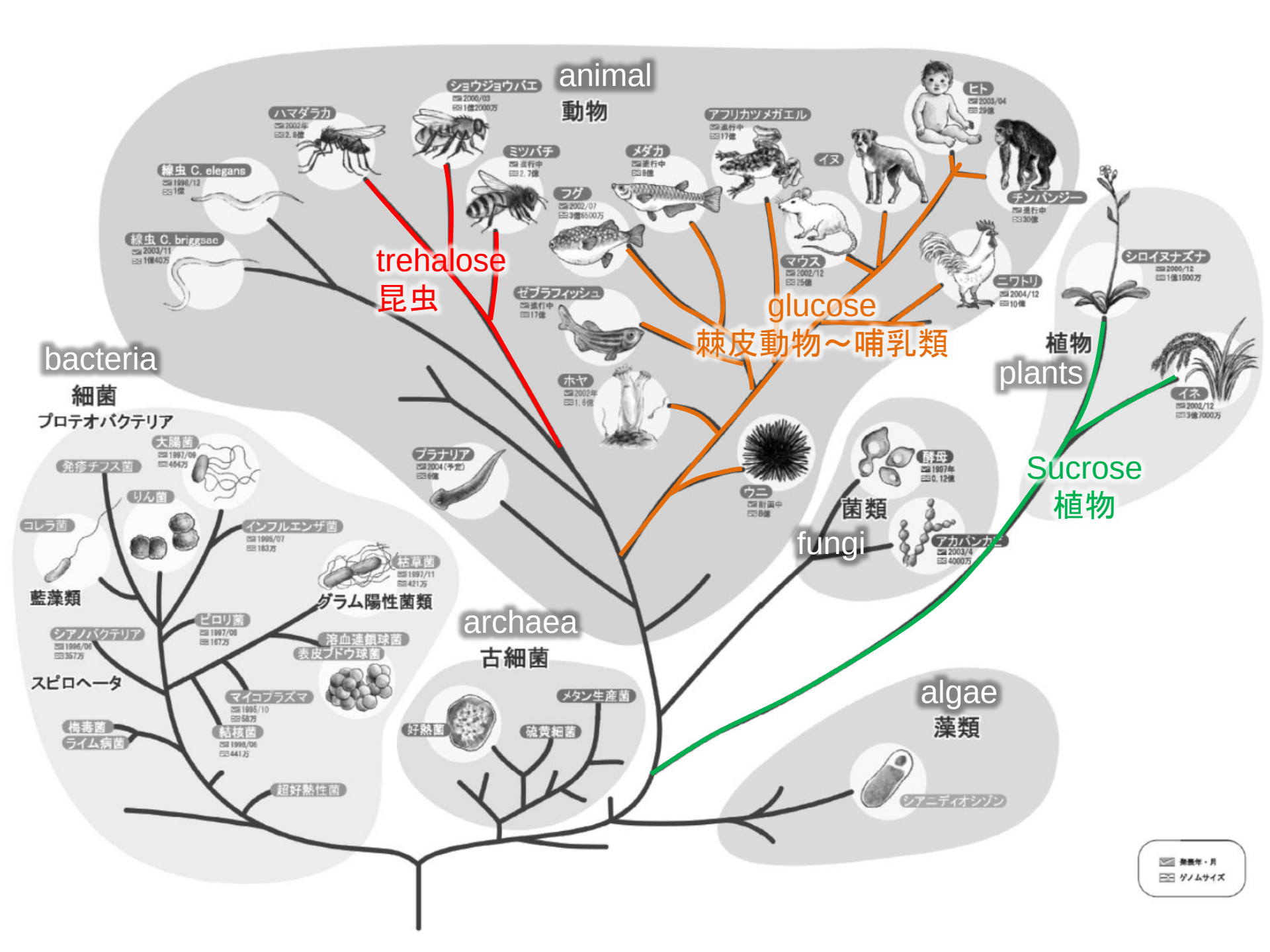
Possible aldoses:
8 x 2 (D-GA or L-GA)
= 16 kinds

L-GAの場合も同じ4種のアルドール縮合生成物ができる

Stable hexoses were chosen by life

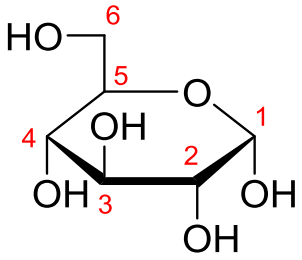


2001 Viva Origino 119.

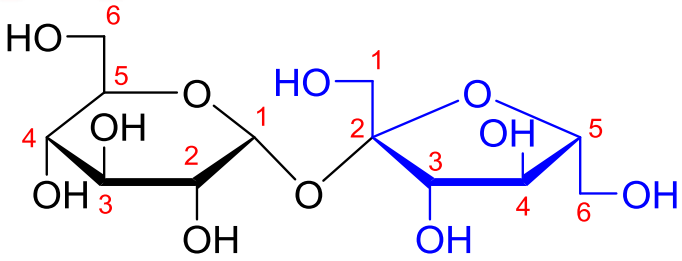

animal
動物
trehalose
昆虫
glucose
棘皮動物～哺乳類
bacteria
細菌
プロテオバクテリア
藍藻類
スピロヘータ
グラム陽性菌類
archaea
古細菌
plants
植物
Sucrose
植物
fungi
菌類
algae
藻類
ハマダラカ
ショウジョウバエ
ミツバチ
線虫 C. elegans
線虫 C. briggsae
フグ
メダカ
アフリカツメガエル
イヌ
ヒト
チンパンジー
マウス
ニワトリ
ゼブラフィッシュ
ホヤ
ウニ
プラナリア
シロイヌナズナ
イネ
酵母
アカパンカビ
シアニディオシゾン
大腸菌
発疹チフス菌
りん菌
コレラ菌
インフルエンザ菌
枯草菌
ピロリ菌
シアノバクテリア
溶血連鎖球菌
表皮ブドウ球菌
マイコプラズマ
梅毒菌
ライム病菌
結核菌
超好熱性菌
好熱菌
硫黄細菌
メタン生産菌

Energy media in vessels of multicellular organisms
多細胞生物のエネルギーメディア

Non-reducing sugars were chosen !

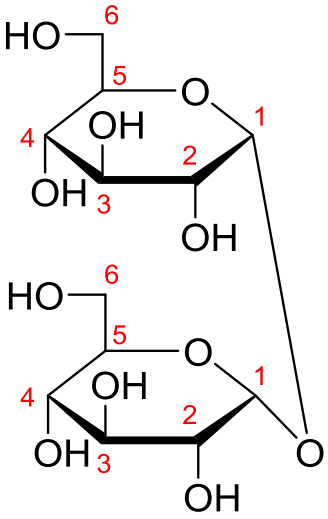


glucose



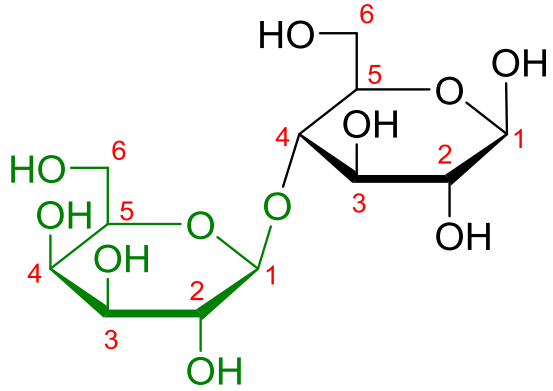
sucrose

α-D-glucopyranosyl-(1->2)-β-D-fructofuranoside



trehalose

α-D-glucopyranosyl-(1->1)-α-D-glucopyranoside



lactose

β-D-galactopyranosyl-(1->4)-D-glucose

Quiz:

For diabetes, please ask questions from the standpoint of evolutionary medicine and suggest a cure.

糖尿病について、進化医学の立場から質問をし、治療法を提案してください。