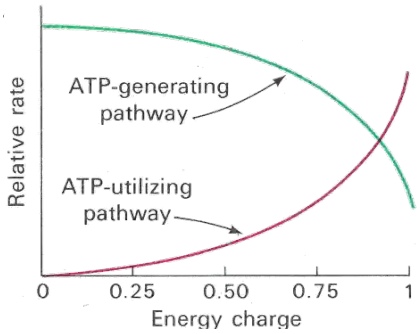
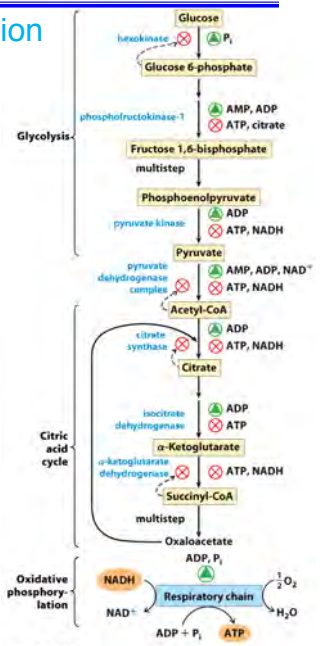
# Oxidative Phosphorylation

- Primarily regulated by substrate availability
  - $NAD^+$ and $ADP/P_i$
- Inhibition of OxPhos leads to accumulation of NADH.
  - causes feedback inhibition cascade up to PFK-1 in Glycolysis




Regulation



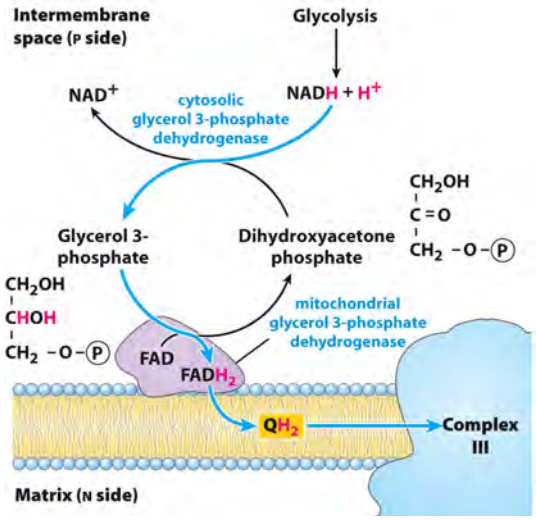

# Oxidative Phosphorylation

## Converting Cytosolic Electron Carriers (NADH) to the Mitochondria

### Glycerol-3-Phosphate Shuttle

### Malate-Aspartate Shuttle

- This more complicated shuttle is mostly present in liver, heart, and kidney.
- Will be discussed when we do amino-acid degradation
- It moves NADH equivalents form cytosol to NADH equivalents to the mitochondria.



# Oxidative Phosphorylation

## Net Production of ATP via Catabolic Pathways

**TABLE 19-5 ATP Yield from Complete Oxidation of Glucose**

| Process | Direct product | Final ATP |
|---|---|---|
| Glycolysis | 2 NADH (cytosolic)<br>2 ATP | 3 or 5[a]<br>2 |
| Pyruvate oxidation (two per glucose) | 2 NADH (mitochondrial matrix) | 5 |
| Acetyl-CoA oxidation in citric acid cycle (two per glucose) | 6 NADH (mitochondrial matrix)<br>2 $FADH_2$<br>2 GTP | 15<br>3<br>2 |
| Total yield per glucose | | 30 or 32 |

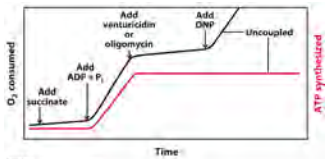
[a]If the malate/aspartate shuttle is used to transfer reducing equivalents into the mitochondrion, yield is 5 ATP. If the glycerol 3-phosphate shuttle is used, the yield is 3 ATP.

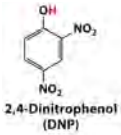
# Oxidative Phosphorylation

## UNCOUPLING

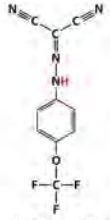
Chemically uncoupling ET and ATP biosynthesis:

Recall:



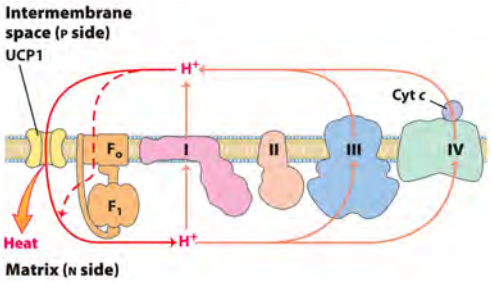




2,4-Dinitrophenol (DNP)




Carbonylcyanide-*p*-trifluoromethoxyphenylhydrazone (FCCP)

- In addition to chemical uncouplers (DNP & FCCP), there are times when uncoupling is needed physiologically
- Uncoupling protein 1 (UCP-1) in babies
- Hibernating animals



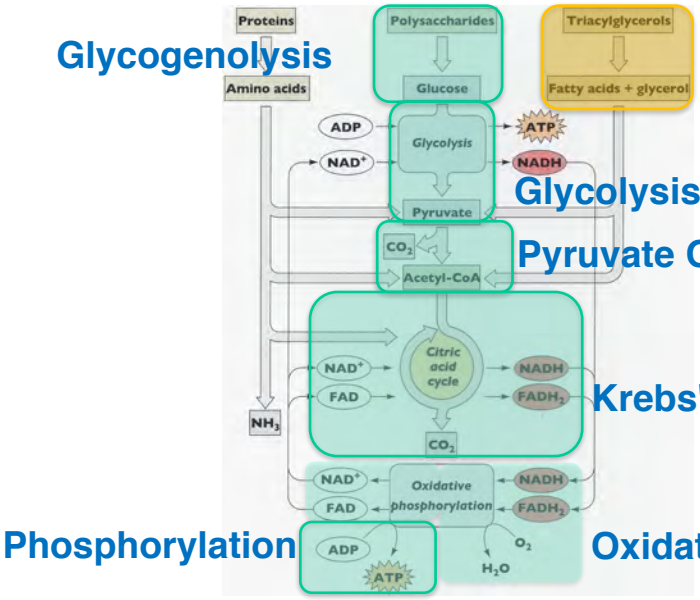
## Summary:Oxidative Phosphorylation

We learned that:

- the reduced cofactors pass electrons into the electron- transport chain in mitochondria
- stepwise electron transport is accompanied by the directional transport of protons across the membrane against their concentration gradient
- the energy in the electrochemical proton gradient drives synthesis of ATP by coupling the flow of protons via ATP synthase to conformational changes that favor formation of ATP in the active site

# Lipid Degradation

# Lipid Degradation: Fatty Acids




Glycogenolysis

Fat Catabolism

Glycolysis

Pyruvate Oxidation

Krebs' Cycle

Phosphorylation

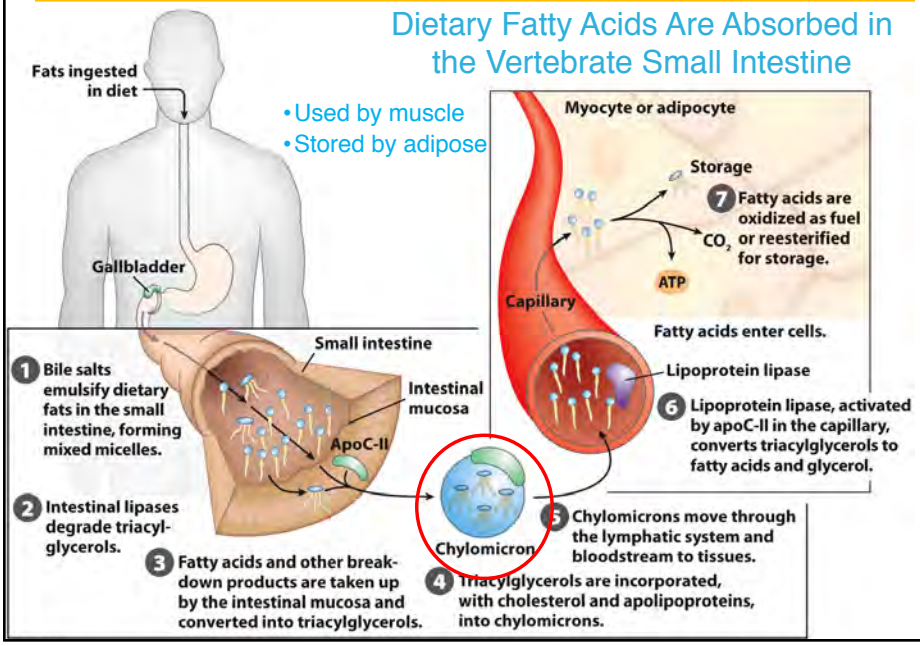
Oxidative

# Fatty Acid Degradation

- Fat as a fuel; ingestion of the “chunks”
- How fats are mobilized and transported in animal tissues
- COMPARTMENTATION
  - How fats are oxidized in mitochondria
    - Glycerol
    - Saturated Fatty Acids
    - Un-saturated Fatty Acids
    - Odd-chain Fatty Acids
  - Blocks to oxidation in mitochondria: How “ketone bodies” are utilized
  - Fatty-acid metabolism in other organelles

# Fatty Acid Degradation

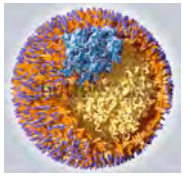
## Dietary Fatty Acids Are Absorbed in the Vertebrate Small Intestine

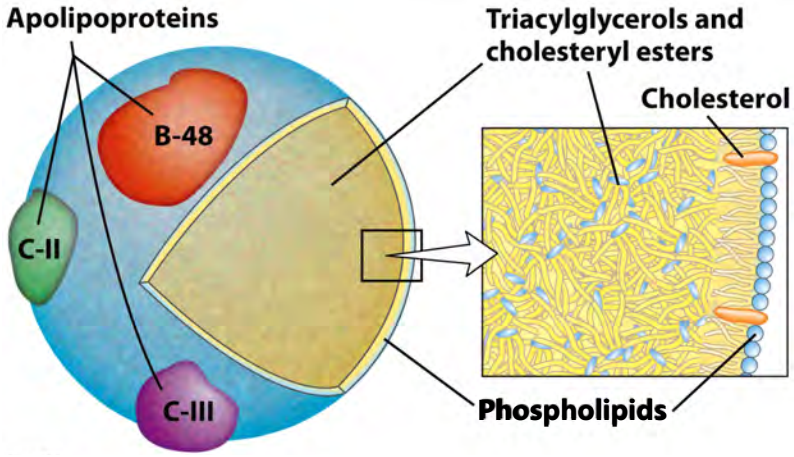



- Used by muscle
- Stored by adipose

# Fatty Acid Degradation

## Chylomicrons





# Fatty Acid Degradation

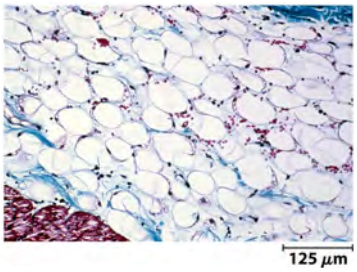
- Fatty Acid Oxidation is a Major Energy Source
- About one-third of human energy needs comes from dietary triacylglycerols (fat).
- There are differences in tissue utilization. About 80% of energy needs of mammalian heart and liver are met by oxidation of fatty acids.
- Many hibernating animals, such as grizzly bears, rely almost exclusively on fats as their source of energy.

There are FOUR stages in the catabolism of lipids:

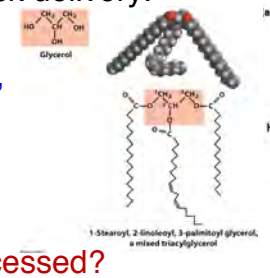
1) Mobilization from tissues (mostly adipose)
2) Activation of fatty acids
3) Transport
4) Oxidation

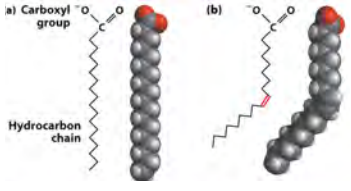
# Fatty Acid Degradation

- Fuel Storage of Fat is efficient
- The advantage of fats over polysaccharides:
  - Fatty acids carry more energy per carbon because they are more reduced.
  - Fatty acids complex or carry less water because they are nonpolar.




- Glucose and glycogen are for short-term energy needs and quick delivery.
- Fats are for long-term (months) energy needs, storage, and have slow delivery.



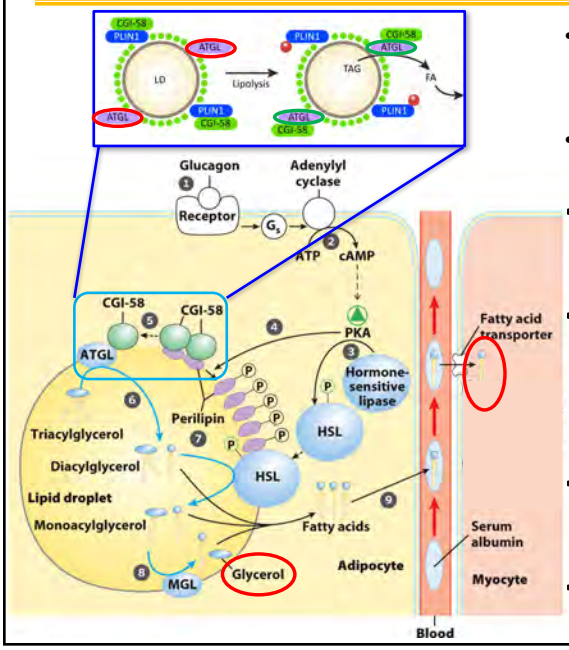




Fatty acids come in all types: ± double bonds, long & short, odd & even, etc.

- How are fat stores accessed?

# Fatty Acid Degradation

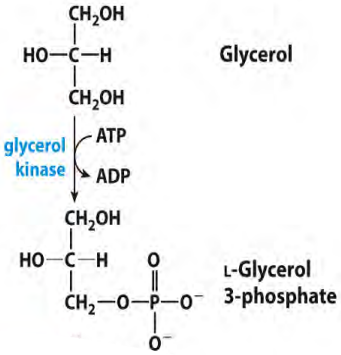
Mobilization




- Stored Triacylglycerides are released in response to Hormone signals
- Hormones trigger a mobilization "cascade" that activates lipases
- Lipases are activated by hormones glucagon and epinephrine. ❶ ❷❸❹
- In the case of glucagon, Protein Kinase A (**PKA**) is activated, ❺❼ which leads to the progressive activation of 3 lipases, one for each position on glycerol. ❸❻❽
- Fats are degraded into fatty acids and glycerol in the cytoplasm of adipocytes. ❽❾
- Fatty acids are transported to other tissues through the blood.

# Fatty Acid Degradation

- Glycerol is a sugar alcohol and is converted to a glycolytic intermediate
- Glycerol kinase activates glycerol at the expense of ATP.
- Subsequent reactions recover more than enough ATP to cover this cost.
- Allows limited anaerobic catabolism of fats
- A redox reaction is required to convert the alcohol to a ketone. Done by glycerol-3-phosphate dehydrogenase
- We'll see this reaction again in lipid synthesis



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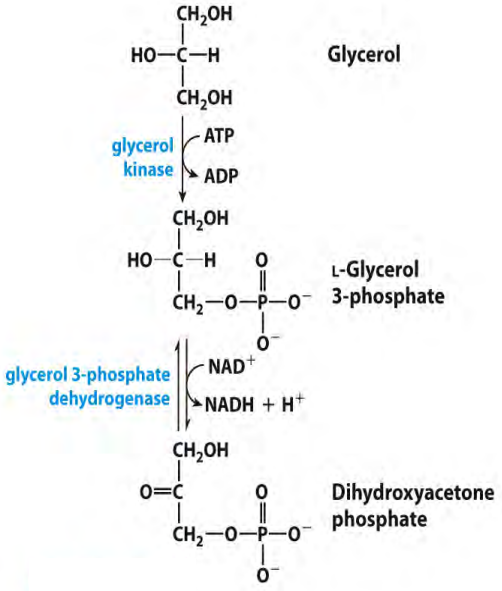
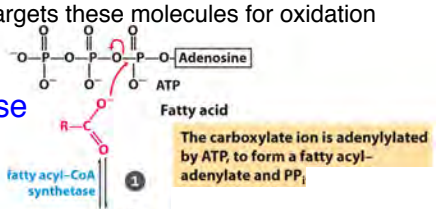



# Fatty Acid Degradation

Activation

- Like the activation of sugars by phosphorylation, fatty acids must also be activated.
- Not having any alcohol groups, esterification of the carboxylate is the only chemistry available.
- A thio-ester is a higher energy bond than a simple ester: use Coenzyme A.
- Conversion to Fatty Acyl-CoA targets these molecules for oxidation

Fatty acyl–CoA synthetase



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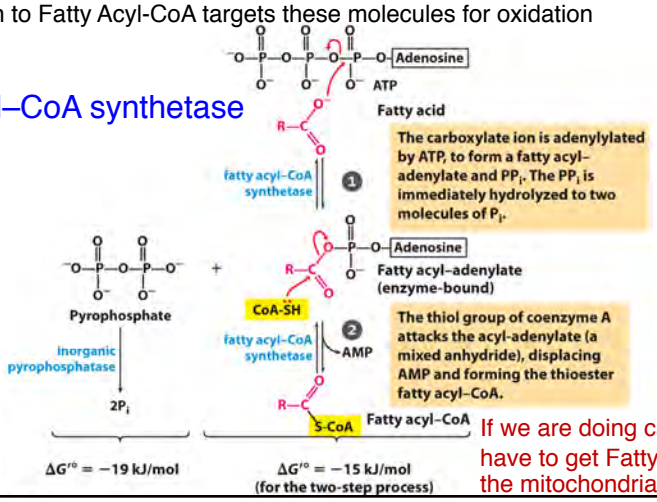


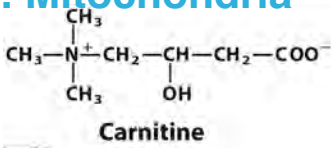

If we are doing catabolism, we have to get Fatty-acyl CoA into the mitochondria.

# Fatty Acid Degradation

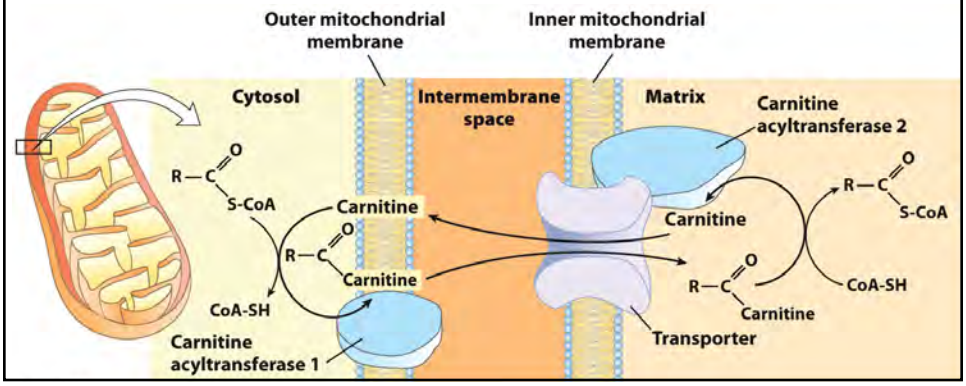
Transport

## COMPARTMENTATION: Mitochondria

Acyl-Carnitine/Carnitine Transport



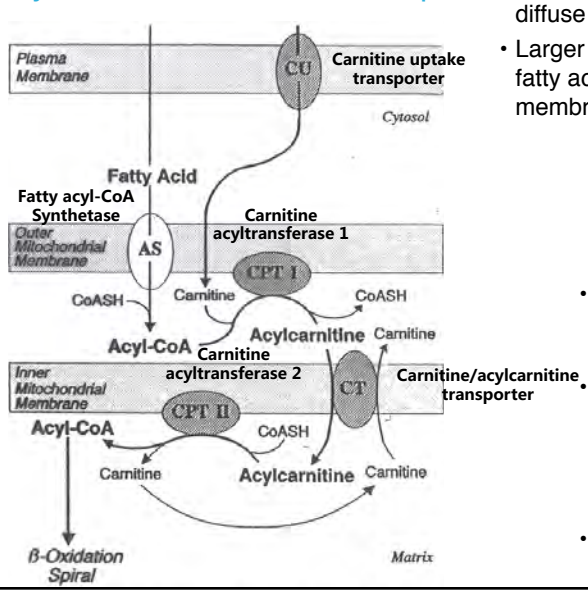

- $\beta$ oxidation of fatty acids occurs in mitochondria.
- Fatty acyl-CoAs are transported via acyl-carnitine/carnitine transporter.



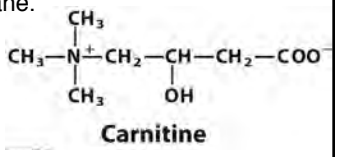
# Fatty Acid Degradation

Transport

## Acyl-Carnitine/Carnitine Transport




- Small (< 12 carbons) free fatty acids diffuse freely across membranes.
- Larger fatty acids are transported via fatty acid transporters on the plasma membrane.




Carnitine

- Fatty-acyl-CoA Synthetase is attached to the OUTER mitochondrial membrane.
- Recent evidence shows that its associated with an integral membrane transporter: Fatty-acyl Transporter Protein I
- Together, they are indicated on the figure as AS.

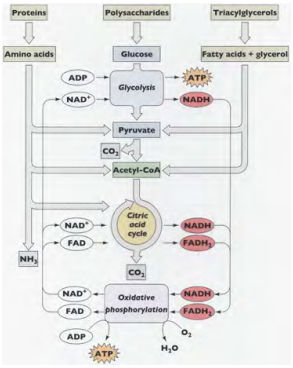
Oxidation

# Degradation of Saturated Fatty Acids

# Fatty Acid Degradation

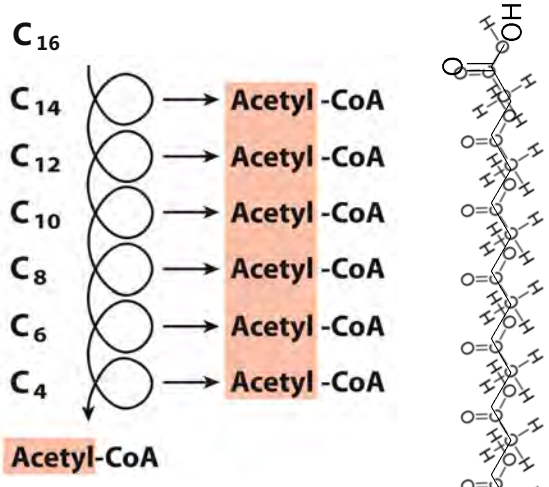
Oxidation

- Fatty Acid Oxidation consists of oxidative conversion of two-carbon units into acetyl-CoA at the $\beta$ carbon of the fatty acid with concomitant generation of NADH and $FADH_2$.
  - –involves oxidation of $\beta$ carbon to thioester of fatty acyl-CoA
- The acetyl-CoA is converted into $CO_2$ via citric acid cycle with concomitant generation NADH and $FADH_2$. The NADH and $FADH_2$ are re-oxidized via the electron transport down the respiratory chain, and conversion into ATP.
- CONVERGENT PATHWAY with GLUCOSE.



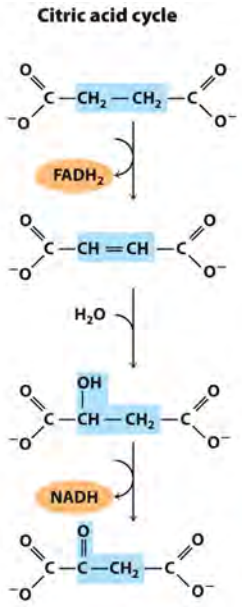

# Fatty Acid Degradation

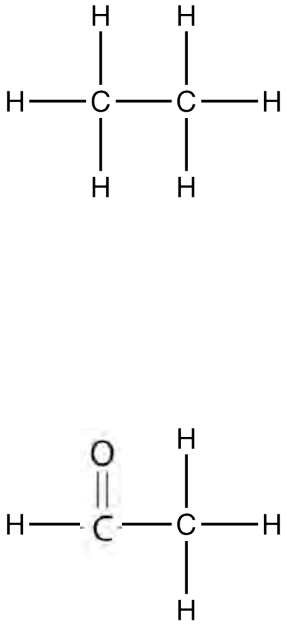
acetic acid ($C_2$)




palmitic acid ($C_{16}$)

# Fatty Acid Degradation



# Fatty Acid Degradation