CHAPTER 17: Citric Acid Cycle
(Krebs cycle)
(TCA or Tri Carboxylic Acid cycle)

Glycolysis: glucose $\longrightarrow$ pyruvate

intermediate step: pyruvate + CoA $\longrightarrow$ acetyl CoA

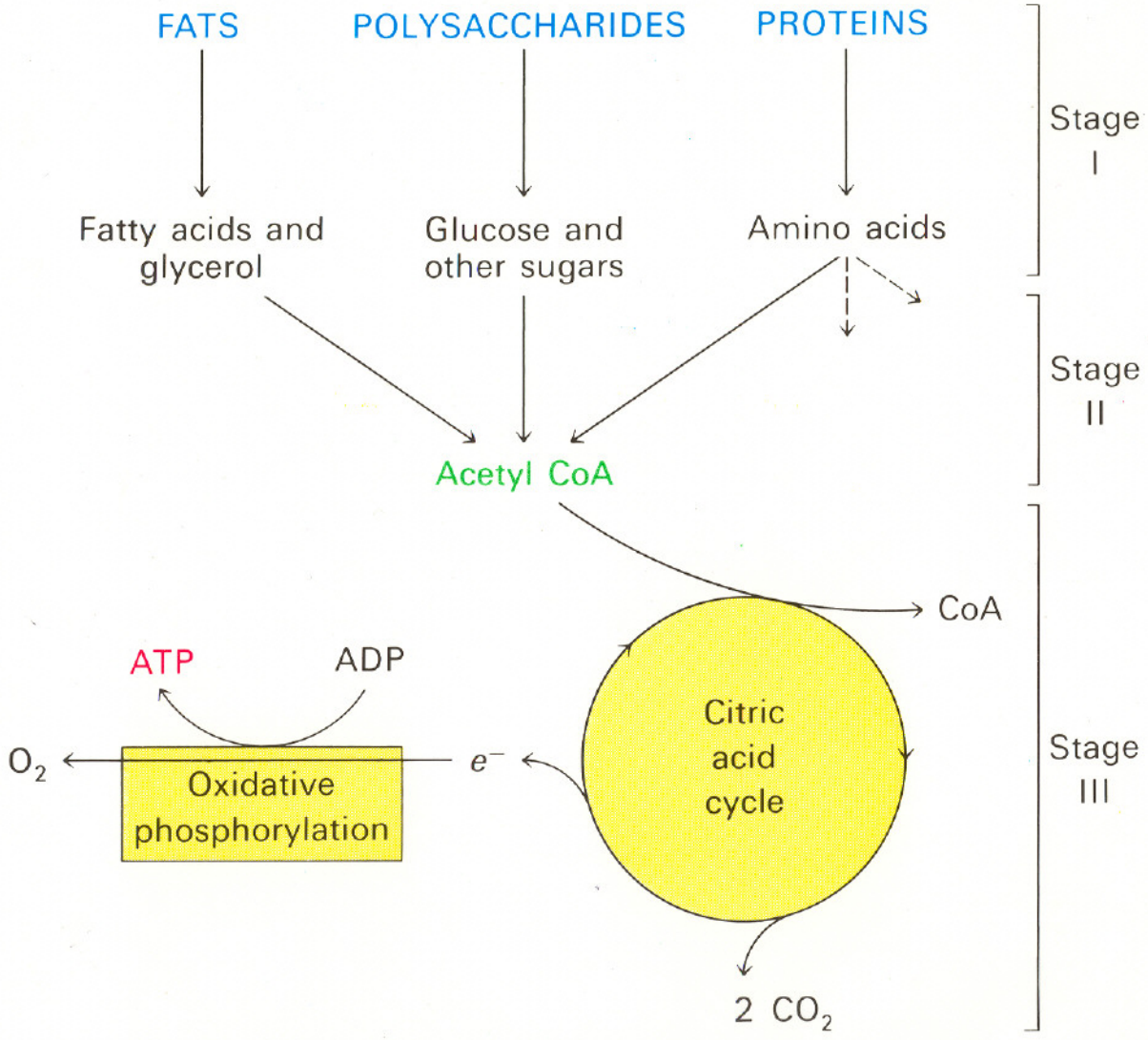
Citric acid cycle: acetyl CoA $\longrightarrow$ CO_2 + CoA

The stoichiometry of the citric acid cycle is:

$$\text{Acetyl CoA} + 3\,NAD^+ + FAD + GDP + P_i + 2\,H_2O \longrightarrow$$

$$\longrightarrow 2\,CO_2 + 3\,NADH + FADH_2 + GTP + 2\,H^+ + CoA$$

Stages in the extraction of energy from foodstuffs



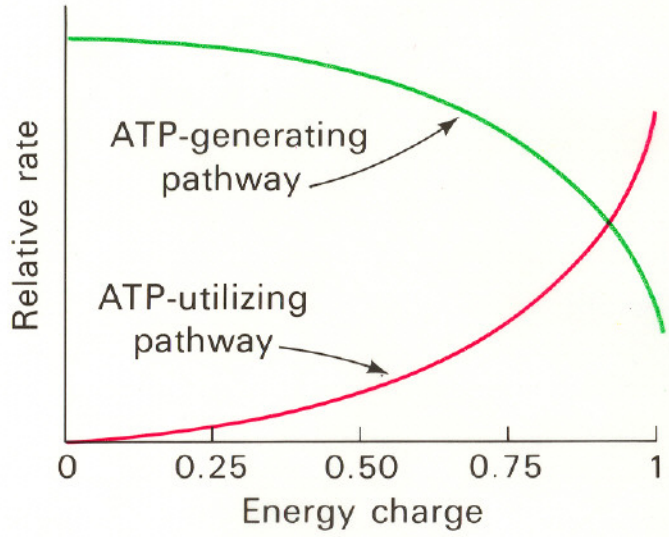


Figure 17-15, page 455; Figure 17-16, page 457

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$$\text{Pyruvate} + \text{CoA} + NAD^+ \longrightarrow \text{acetyl CoA} + CO_2 + NADH$$

pyruvate dehydrogenase complex

(1) $\text{pyruvate} + \text{TPP} \xrightarrow{E_1} \text{hydroxyethyl-TPP} + CO_2$

(2) $\text{hydroxyethyl-TPP} + \text{lipoamide} \xrightarrow{E_1}$

$\longrightarrow$ carbanion of TPP + acetyllipoamide

(3) $\text{acetyllipoamide} + \text{CoA} \xrightarrow{E_2} \text{dihydrolipoamide} +$

$+$ acetyl CoA

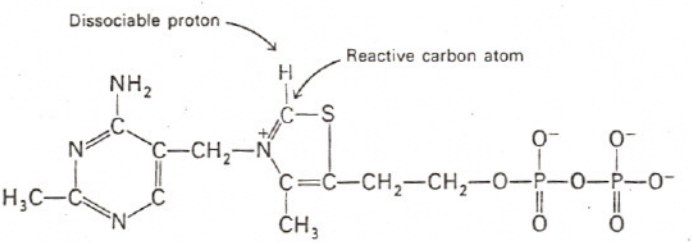
(4) $\text{dihydrolipoamide} + NAD^+ \xrightarrow{E_3} \text{lipoamide} +$

$+ NADH + H^+$

Table 20-2
Pyruvate dehydrogenase complex of *E. coli*

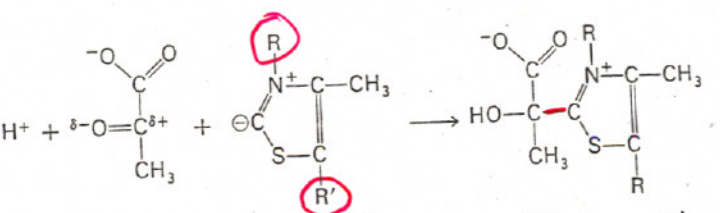
Enzyme	*Abbreviation*	*Number of chains*	*Prosthetic group*	*Reaction catalyzed*
Pyruvate dehydrogenase component	E_1	24	TPP	Oxidative decarboxylation of pyruvate
Dihydrolipoyl transacetylase	E_2	24	Lipoamide	Transfer of the acetyl group to CoA
Dihydrolipoyl dehydrogenase	E_3	12	FAD	Regeneration of the oxidized form of lipoamide

$$\text{Pyruvate} + \text{TPP} \longrightarrow \text{hydroxyethyl-TPP} + CO_2$$

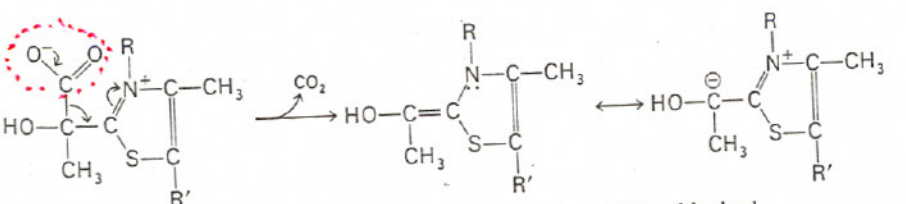


Thiamine pyrophosphate (TPP)

(1)

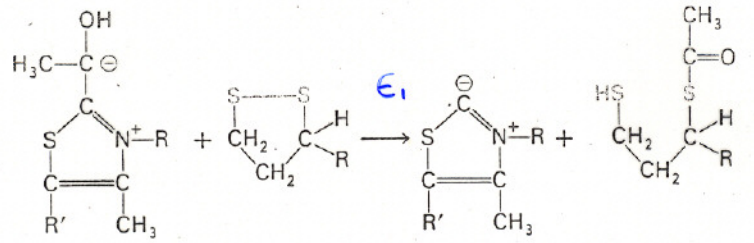


Pyruvate **Carbanion of TPP** **Addition compound**

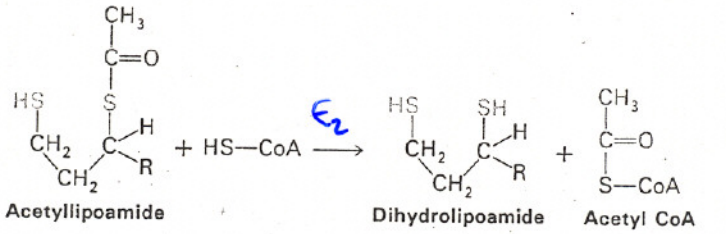


Addition compound **Resonance forms of ionized hydroxyethyl-TPP**

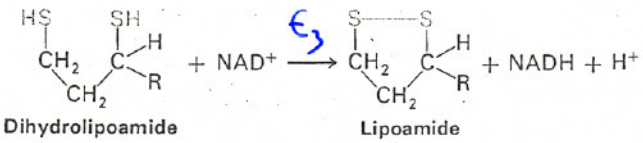
(2)

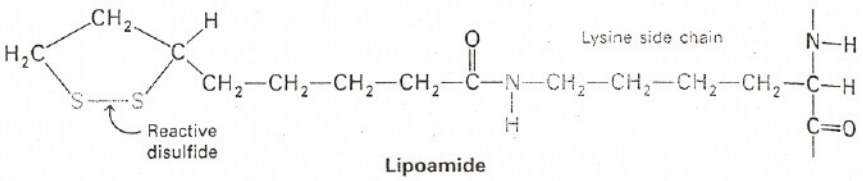

OH
$H_3C-C\ominus$
E_1
CH_3
C=O
HS
Hydroxyethyl-TPP
(Ionized form)
Lipoamide
Carbanion
of TPP
Acetyllipoamide

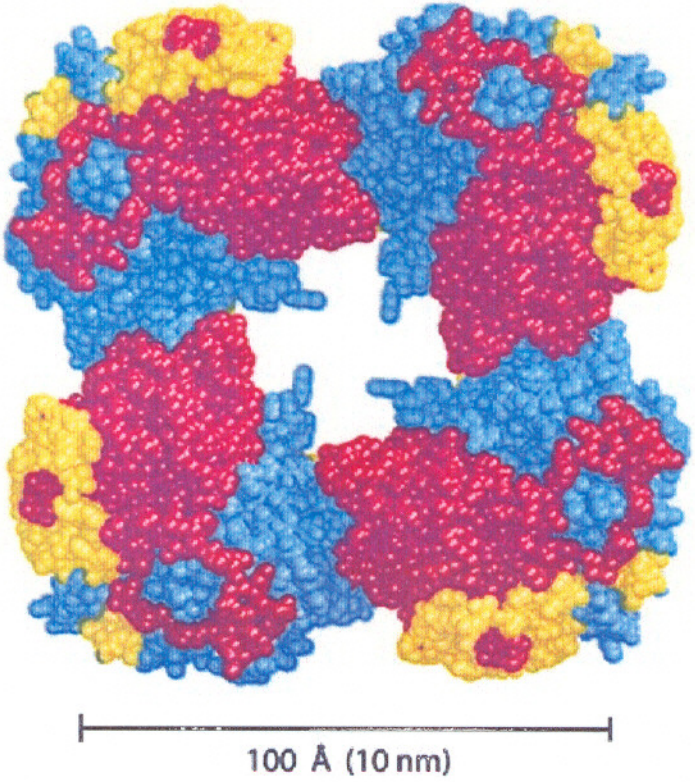
(3)


CH_3
C=O
HS
+ HS—CoA
E_2
SH
S—CoA
Acetyllipoamide
Dihydrolipoamide
Acetyl CoA

(4)


HS
SH
+ NAD^+
E_3
+ NADH + H^+
Dihydrolipoamide
Lipoamide


Lysine side chain
Reactive
disulfide
Lipoamide



Structure of the E_2 transacetylase core of the pyruvate dehydrogenase complex

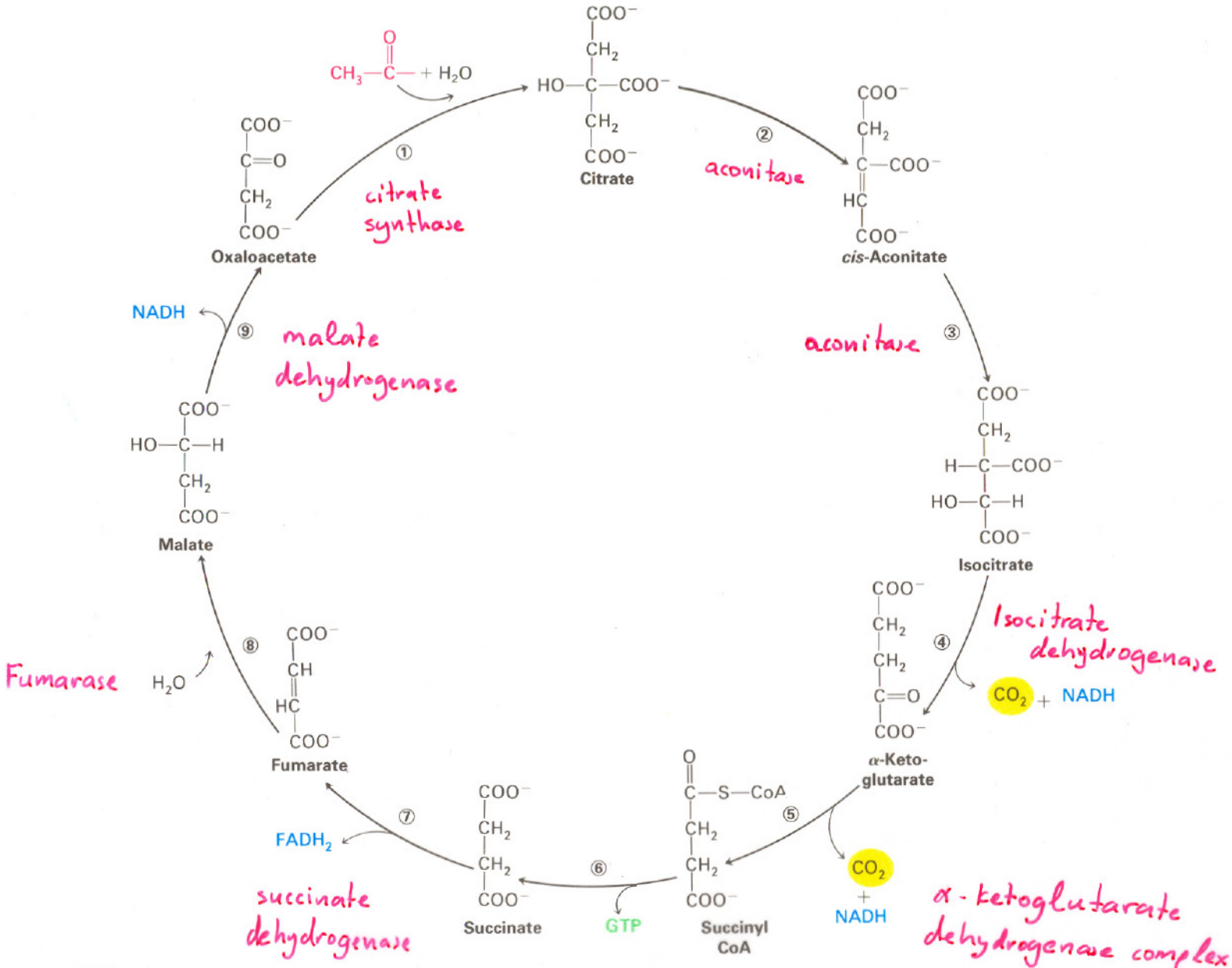


Figure 20-5, page 513

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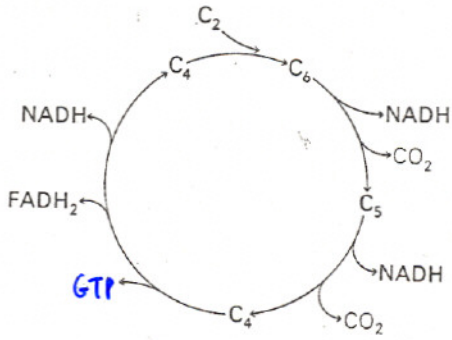
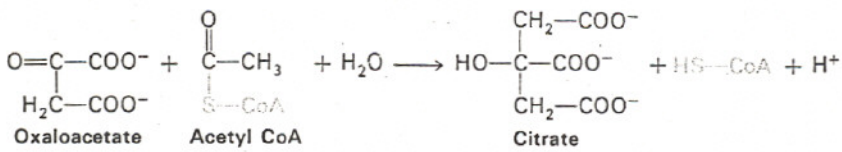
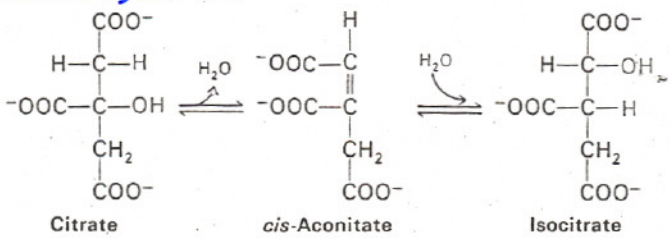


Figure 20-2
An overview of the citric acid cycle.

1. oxaloacetate condenses with acetyl CoA to form citrate

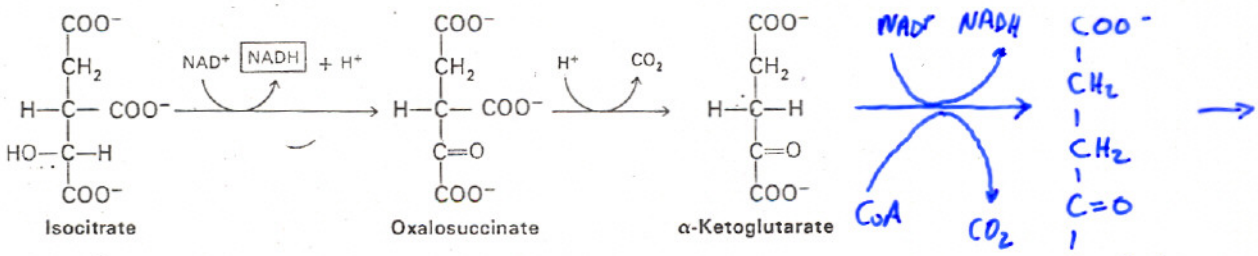


2. citrate is isomerized into isocitrate



3. isocitrate is oxidized and decarboxylated to α-ketoglutarate

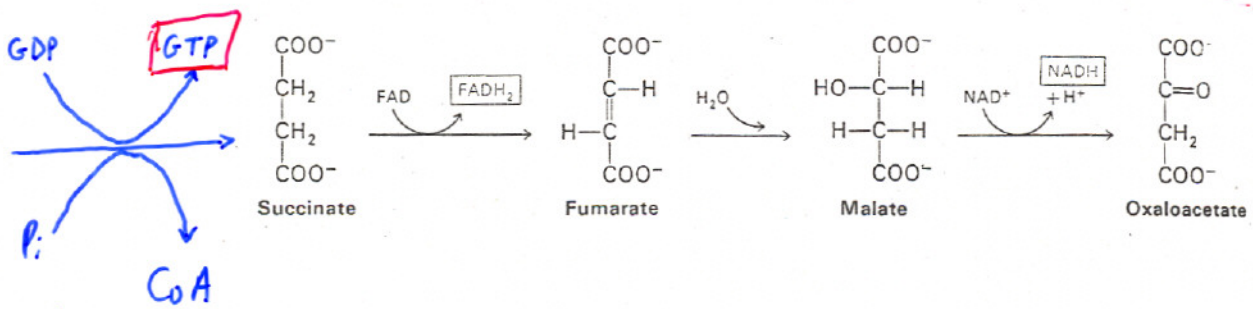
5. oxidative decarboxylation



6. generation of GTP

7-9. oxidation of succinate to oxaloacetate

succinyl CoA



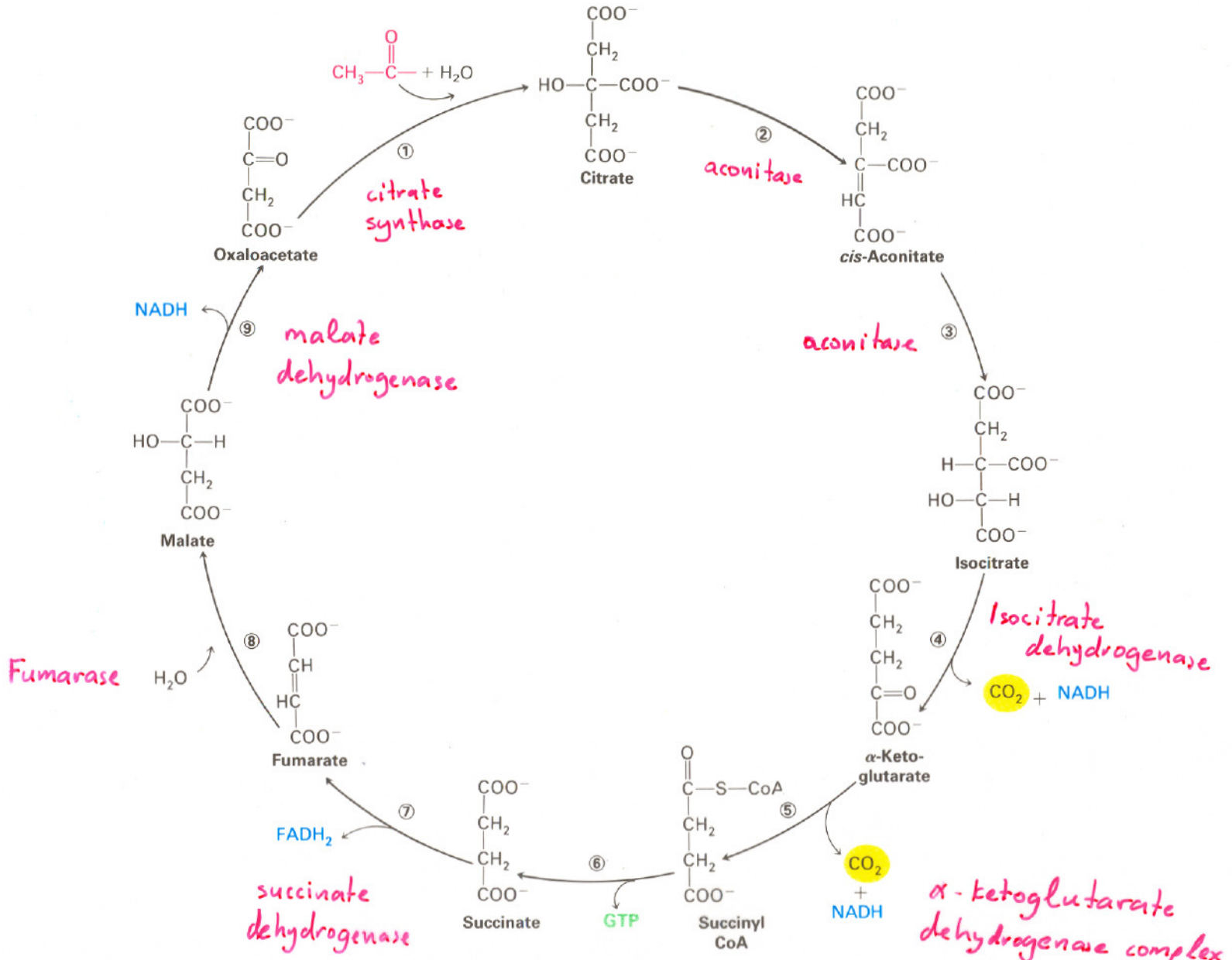


Figure 20-5, page 513

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Step	*Reaction*	*Enzyme*	*Prosthetic group*	*Type**	$\Delta G^{\circ\prime}$
1	Acetyl CoA + oxaloacetate + H_2O $\longrightarrow$ citrate + CoA + H^+	Citrate synthase		a	−7.5
2	Citrate $\rightleftharpoons$ *cis*-aconitate + H_2O	Aconitase	Fe-S	b	+2.0
3	*cis*-Aconitate + H_2O $\rightleftharpoons$ isocitrate	Aconitase	Fe-S	c	−0.5
4	Isocitrate + NAD^+ $\rightleftharpoons$ α-ketoglutarate + CO_2 + NADH	Isocitrate dehydrogenase		d + e	−2.0
5	α-Ketoglutarate + NAD^+ + CoA $\rightleftharpoons$ succinyl CoA + CO_2 + NADH	α-Ketoglutarate dehydrogenase complex	Lipoic acid, FAD, TPP	d + e	−7.2
6	Succinyl CoA + P_i + GDP $\rightleftharpoons$ succinate + GTP + CoA	Succinyl CoA synthetase		f	−0.8
7	Succinate + FAD (enzyme-bound) $\rightleftharpoons$ fumarate + $FADH_2$ (enzyme-bound)	Succinate dehydrogenase	FAD, Fe-S	e	~0
8	Fumarate + H_2O $\rightleftharpoons$ L-malate	Fumarase		c	−0.9
9	L-Malate + NAD^+ $\rightleftharpoons$ oxaloacetate + NADH + H^+	Malate dehydrogenase		e	+7.1

*Reaction type: (a) condensation; (b) dehydration; (c) hydration; (d) decarboxylation; (e) oxidation; (f) substrate-level phosphorylation.

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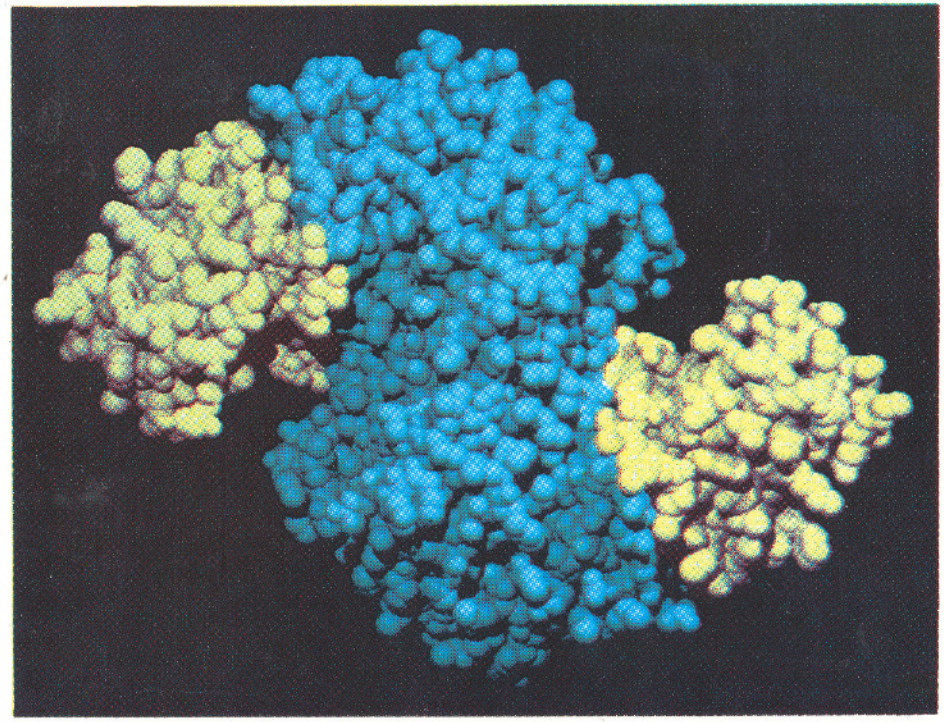
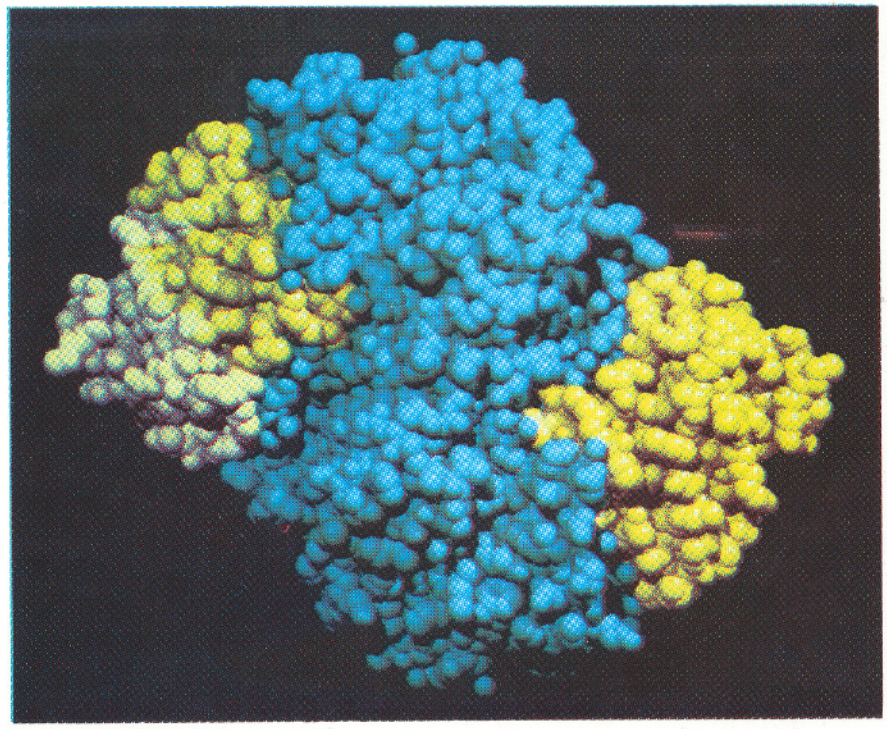
α-ketoglutarate Dehydrogenase Complex

- it catalyzes a reaction similar to the one catalyzed by the pyruvate dehydrogenase complex
- the same cofactors are involved (TPP, lipoamide, CoA, FAD, NAD^+)
- E_1', E_2', E_3'
- "homologous enzyme assemblies"



A open form of enzyme alone



B closed form of the liganded enzyme

Citrate synthase undergoes a large conformational change on binding oxaloacetate. Then it can bind acetyl CoA

- dimer of two identical 49 kDa subunits
- each subunit has two domains (small - yellow, large - blue)

Figure 20-13, page 519

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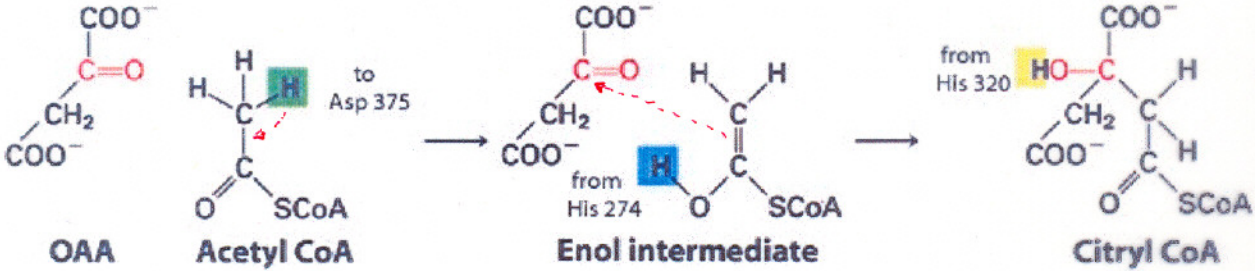

His 274

Asp 375

His 320

Mechanism of synthesis of citryl CoA by citrate synthase

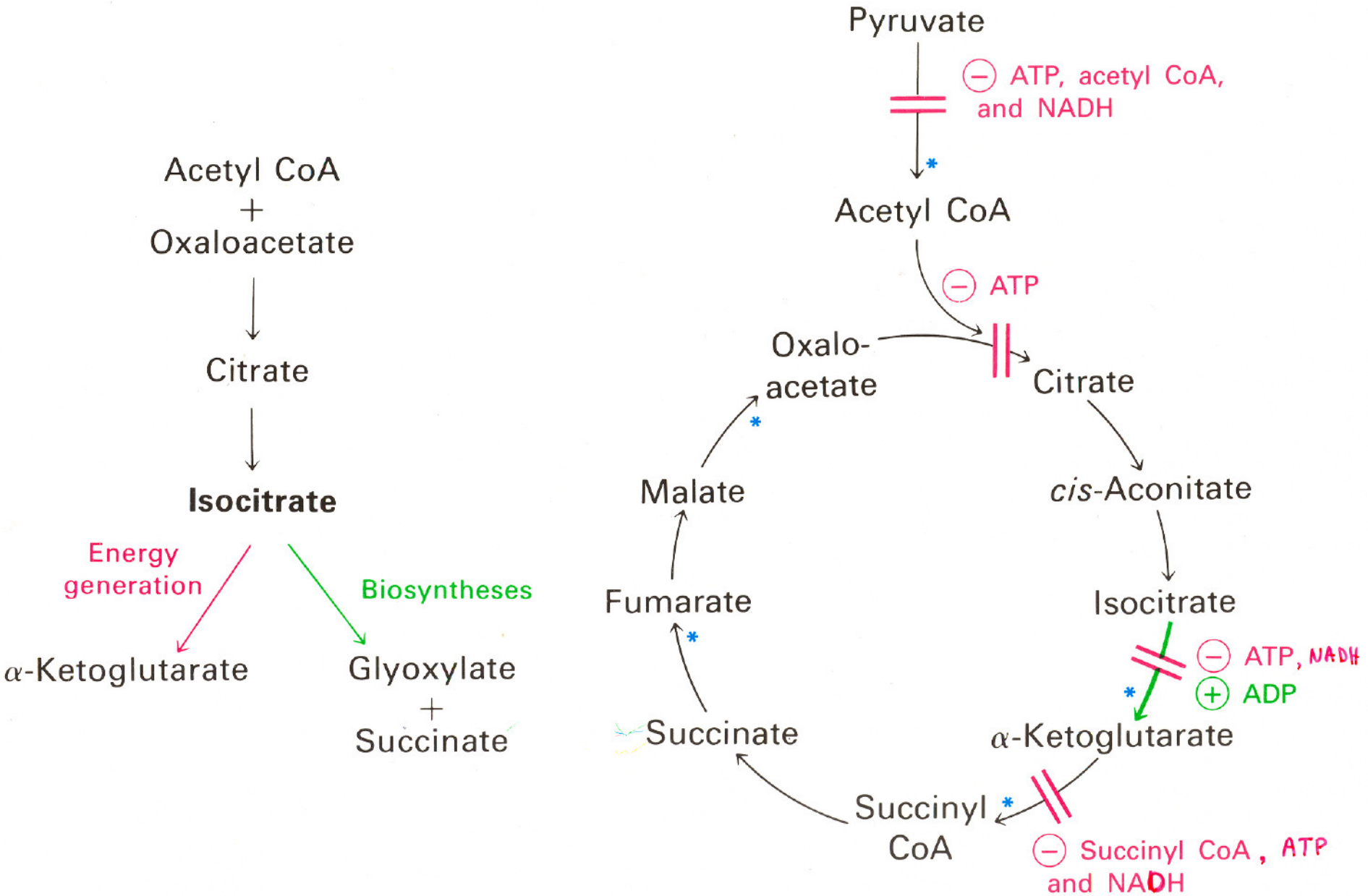

Figure 20-19, page 524; Figure 20-22, page 525

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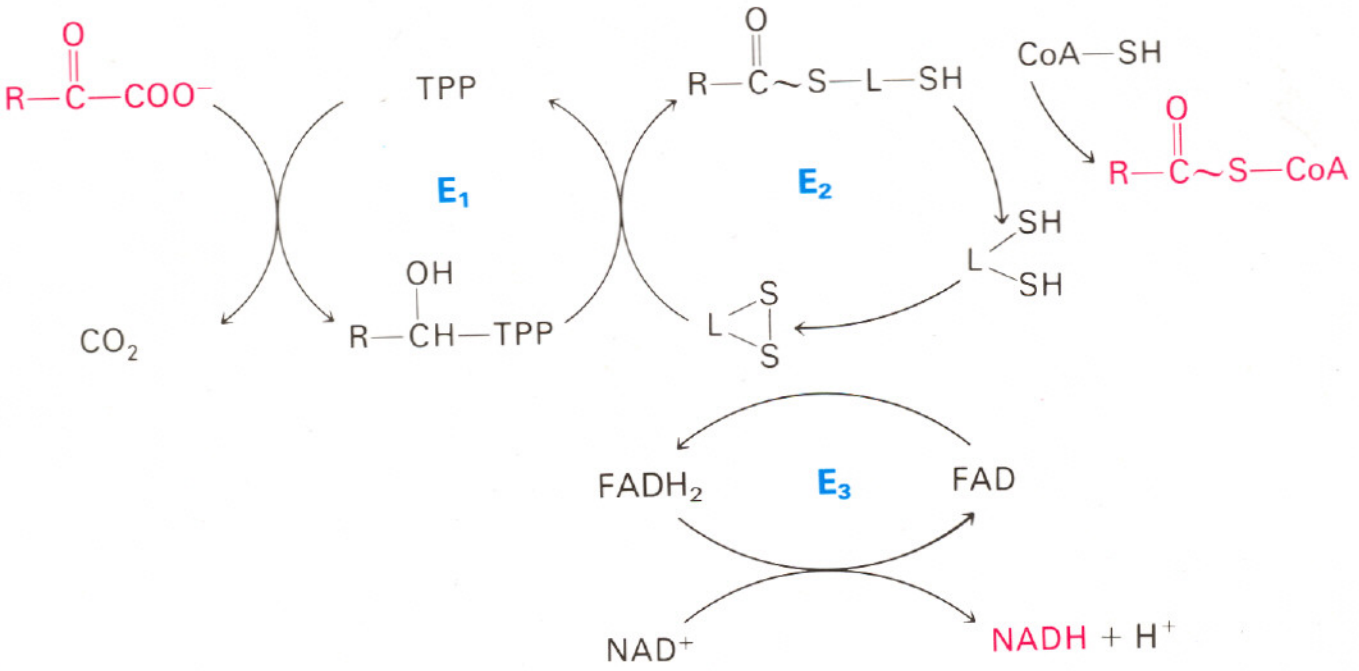
T-61

Set I

CONTROL OF THE TCA CYCLE



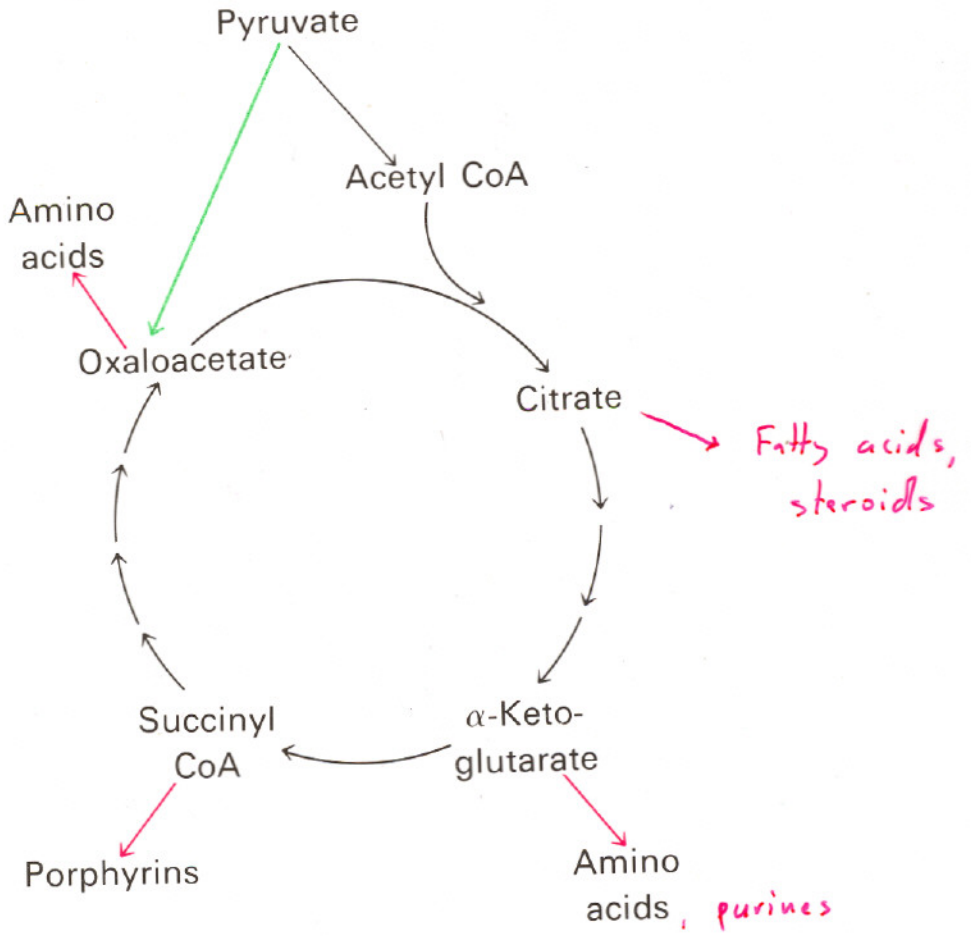


Figure 20-12, page 517; Figure 20-17, page 522

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Beri-Beri

- a neurologic and cardiovascular disorder
- dietary deficiency of thiamine (vitamin B_1)
- major problem in the Far East
  (rice has low content of thiamine)
- TPP is the prosthetic group of
  (i) pyruvate dehydrogenase
  (ii) α-ketoglutarate dehydrogenase
  (iii) transketolase
- TPP utilizes the transfer of an activated aldehyde unit
- it causes increased levels of pyruvate and α-ketoglutarate in blood

CHAPTER 17

PROBLEMS

from textbook # 1, 9, 12, 16

from companion # 1, 3, 8, 9, 13