The Role of the Carnitine System in Human Metabolism

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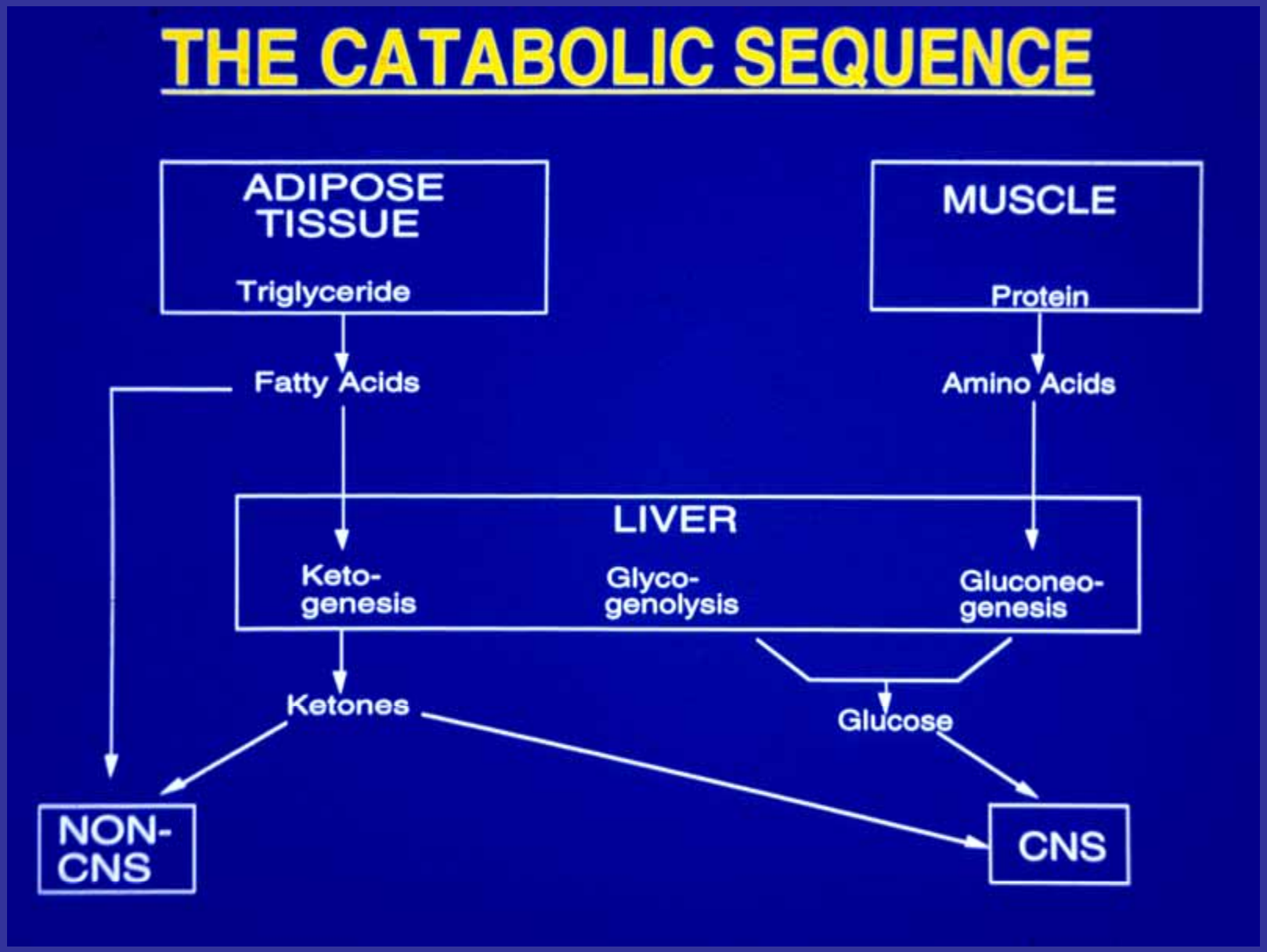
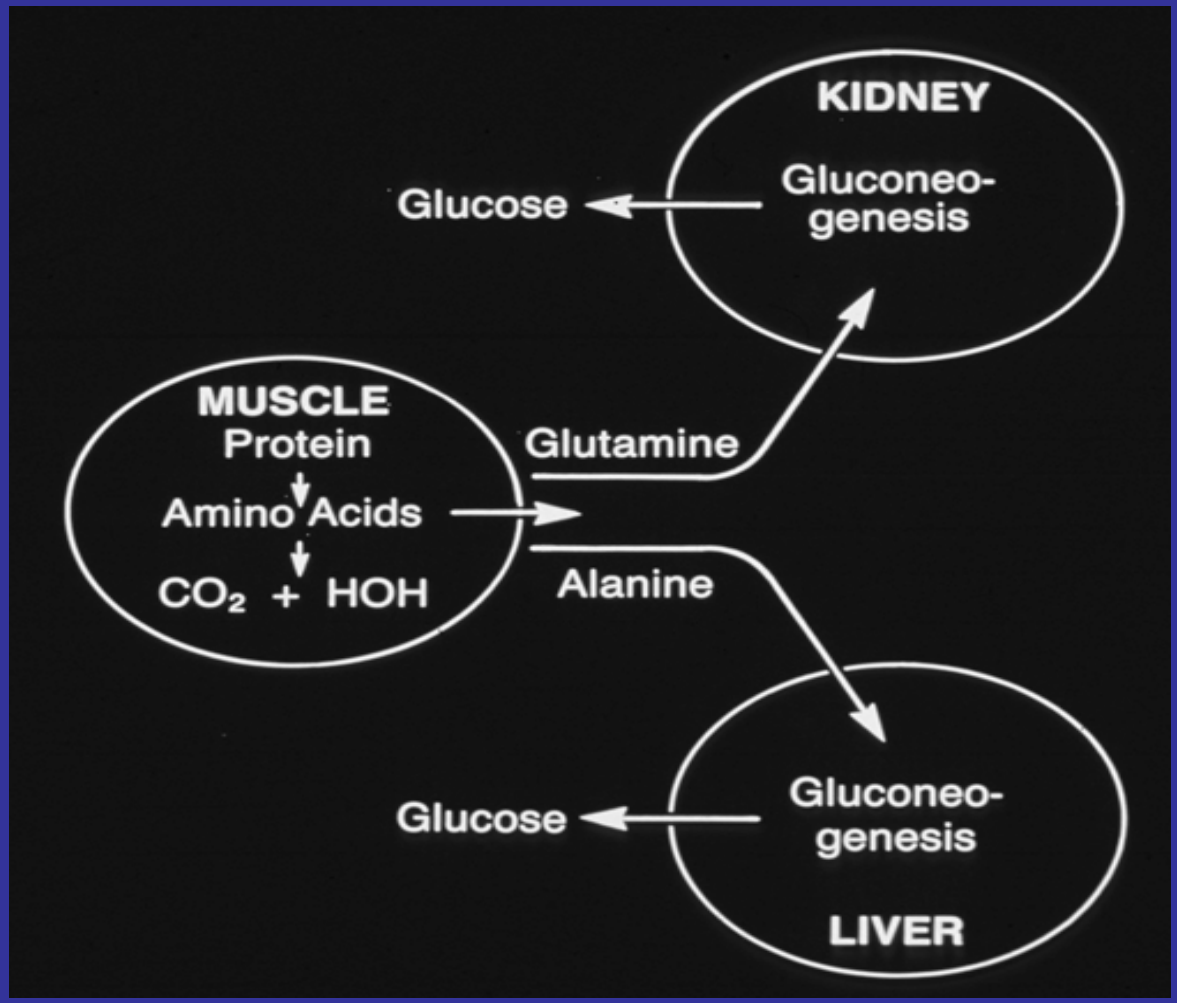
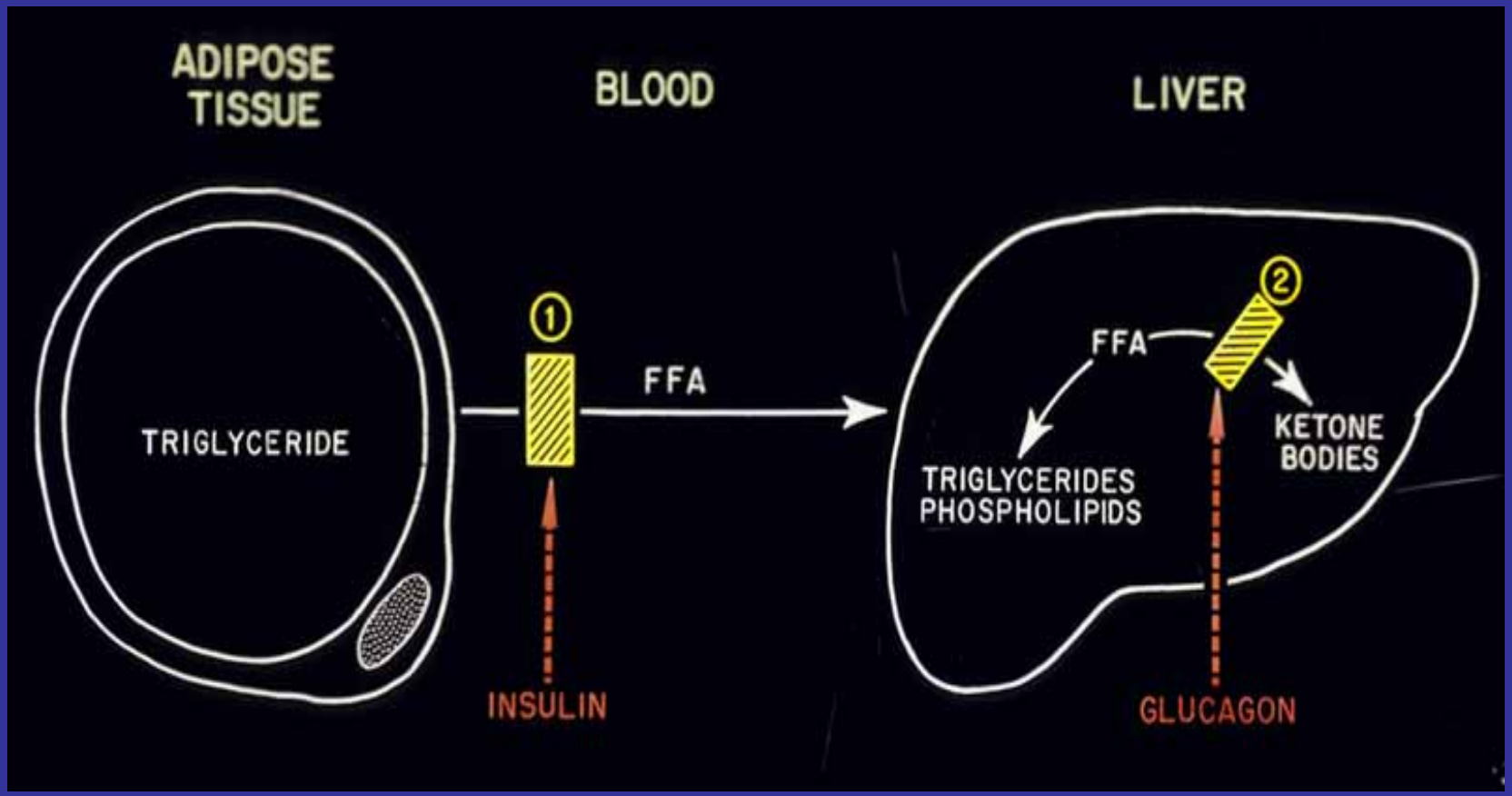

THE CATABOLIC SEQUENCE
ADIPOSE TISSUE
Triglyceride
MUSCLE
Protein
Fatty Acids
Amino Acids
LIVER
Keto-genesis
Glyco-genolysis
Gluconeo-genesis
Ketones
Glucose
NON-CNS
CNS

Gluconeogenesis



Ketone Formation



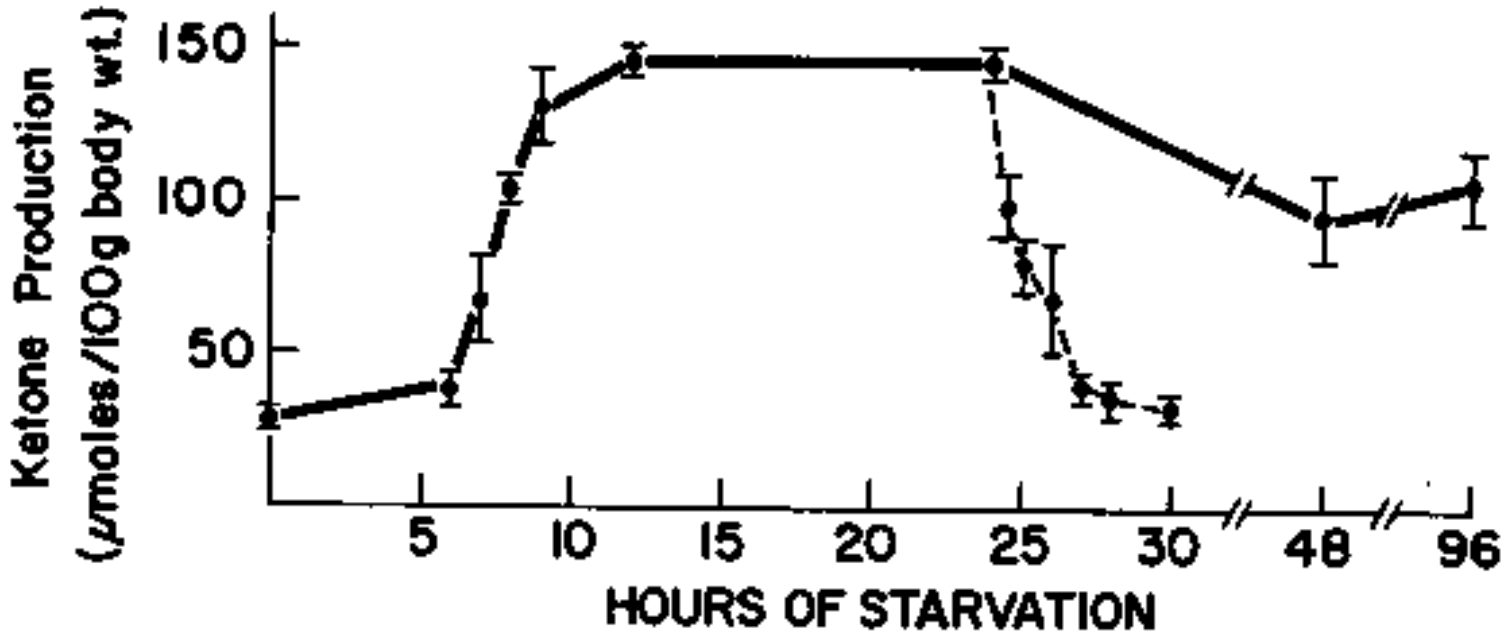


FIGURE 2. The effects of fasting and refeeding on the conversion of oleic acid to ketone bodies in the isolated perfused liver. Rats were fasted for the indicated time and the livers were perfused for 1 h with 0.7 mM oleic acid. The dotted line represents ketone production after refeeding. Major changes in the production of acetoacetate/β-hydroxybutyrate despite fixed levels of fatty acid indicate activation of fatty acid oxidation and ketogenesis. From ref. 7.

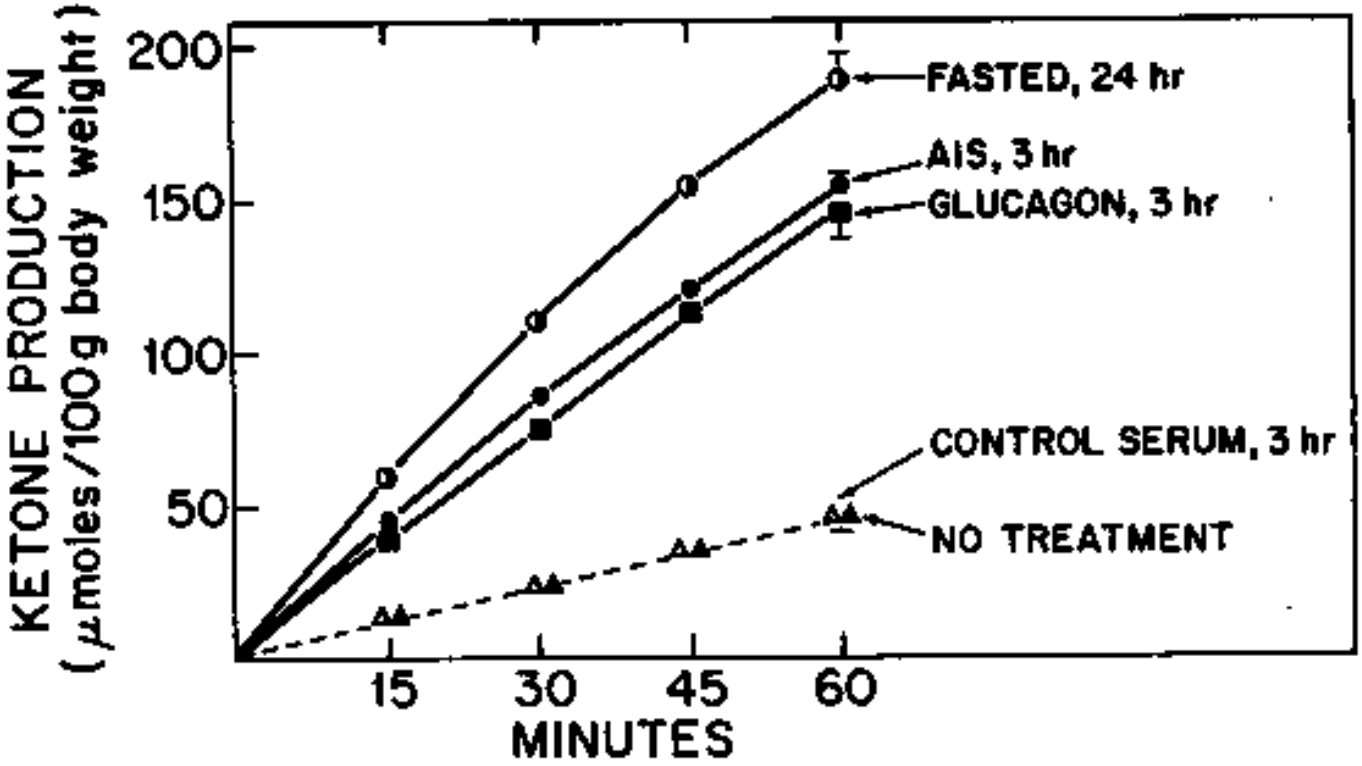
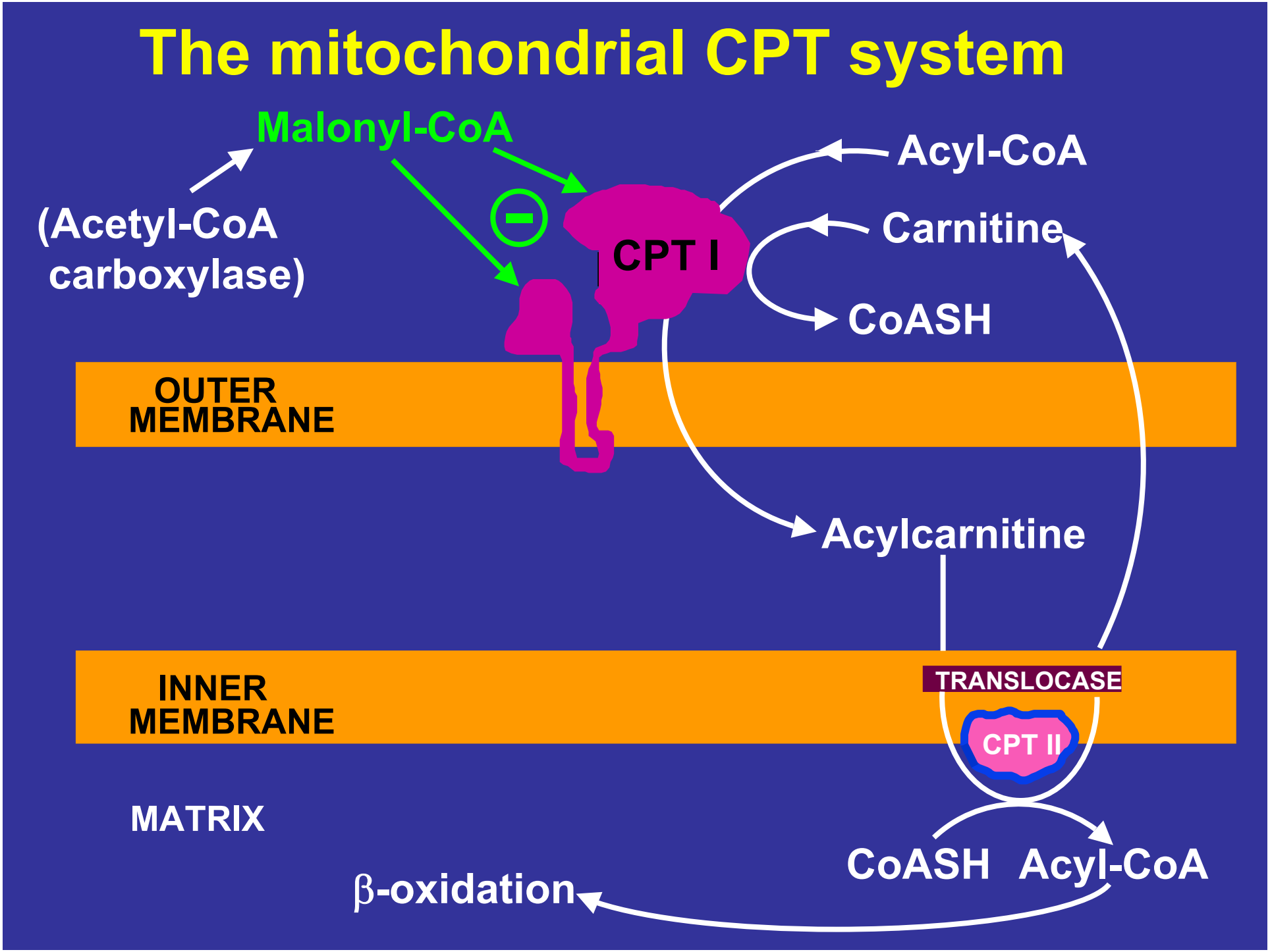


FIGURE 5. Ketone body production in the isolated, perfused liver after treatment of animals with glucagon or anti-insulin serum (AIS). Livers removed from the animals shown in Figure 4 were perfused with 0.7 mM oleic acid. Although glucagon did not cause ketosis in vivo, it activated the ketogenic pathway in liver. See text for details. (Reproduced by permission from McGarry, J. D., Wright, P. H., and Foster, D. W.: Hormonal control of ketogenesis: rapid activation of hepatic ketogenic capacity in fed rats by anti-insulin serum and glucagon. J. Clin. Invest. 1975; 55:1202–1209.)

The mitochondrial CPT system



CPT System Enzymes

	Chromosomal location
CPT-1A (liver)	11 q 13
CPT-1B (muscle)	22 q 13.3
CPT-1C (Brain, testis)*	19 q 13.33
CPT-2 (same all tissues)	1 p 32
CACT (same all tissues)	3 p 21.31

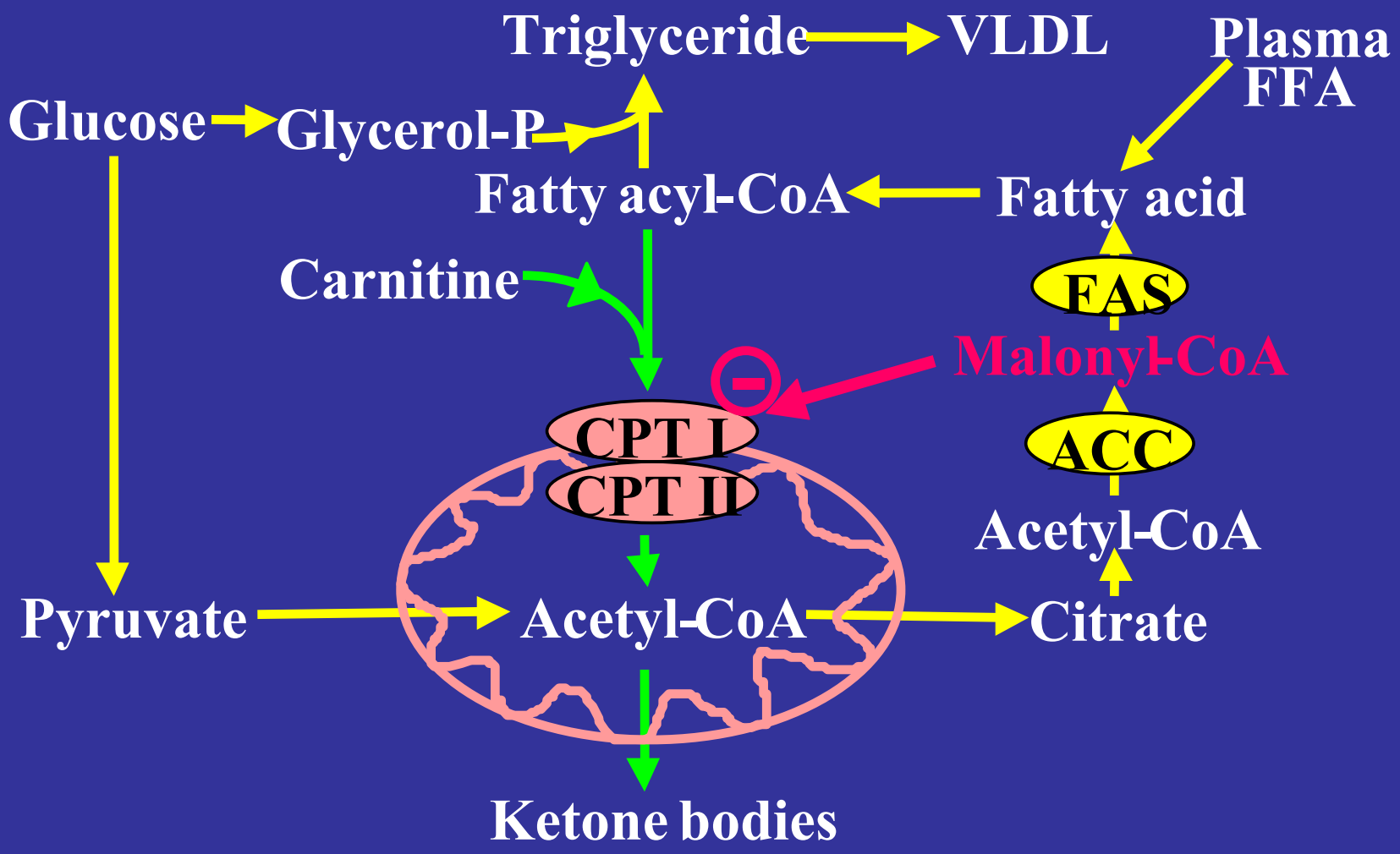
*Mouse CPT-1C is found on chromosome 7

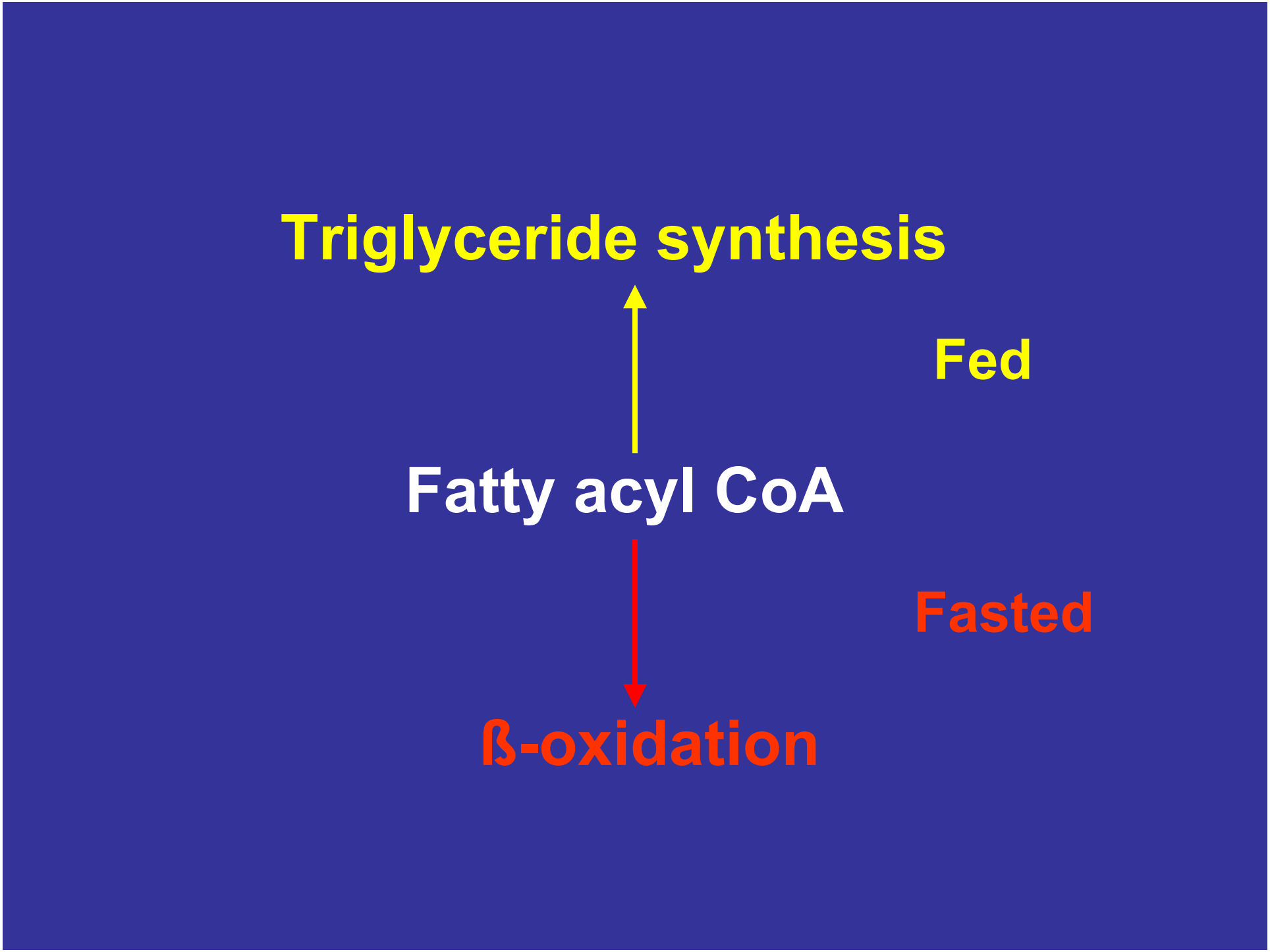
	CPT I	
Tissue	Malonyl-CoA I_{50} (μM)	Carnitine K_m (μM)
Rat liver	1.7	36
Human fetal liver	1.6	39
Rat heart	0.12	167
Guinea pig liver	0.10	270
Human skel. muscle	0.025	480
Rat skel. muscle	0.02	639
Dog skel. muscle	0.01	660
Dog heart	0.01	770

Species	Tissue	Total carnitine content (μmol/gm wet wt)
Rat*	Liver	0.12 ± 0.01
	Kidney cortex	0.23 ± 0.01
	Gastrocnemius muscle	0.46 ± 0.02
	Heart	0.57 ± 0.04
Dog†	Quadriceps muscle	2.6
Human†	Gluteus muscle	3.1
	Erector spinae muscle	3.6
	Quadriceps muscle (a)	2.4
	Quadriceps muscle (b)	2.6
	Pectoralis muscle	2.6

* Values are means ± SEM for six animals.
† Values are from a single determination in different subjects.

FATTY ACID SYNTHESIS AND OXIDATION IN LIVER




Triglyceride synthesis
Fed
Fatty acyl CoA
Fasted
ß-oxidation

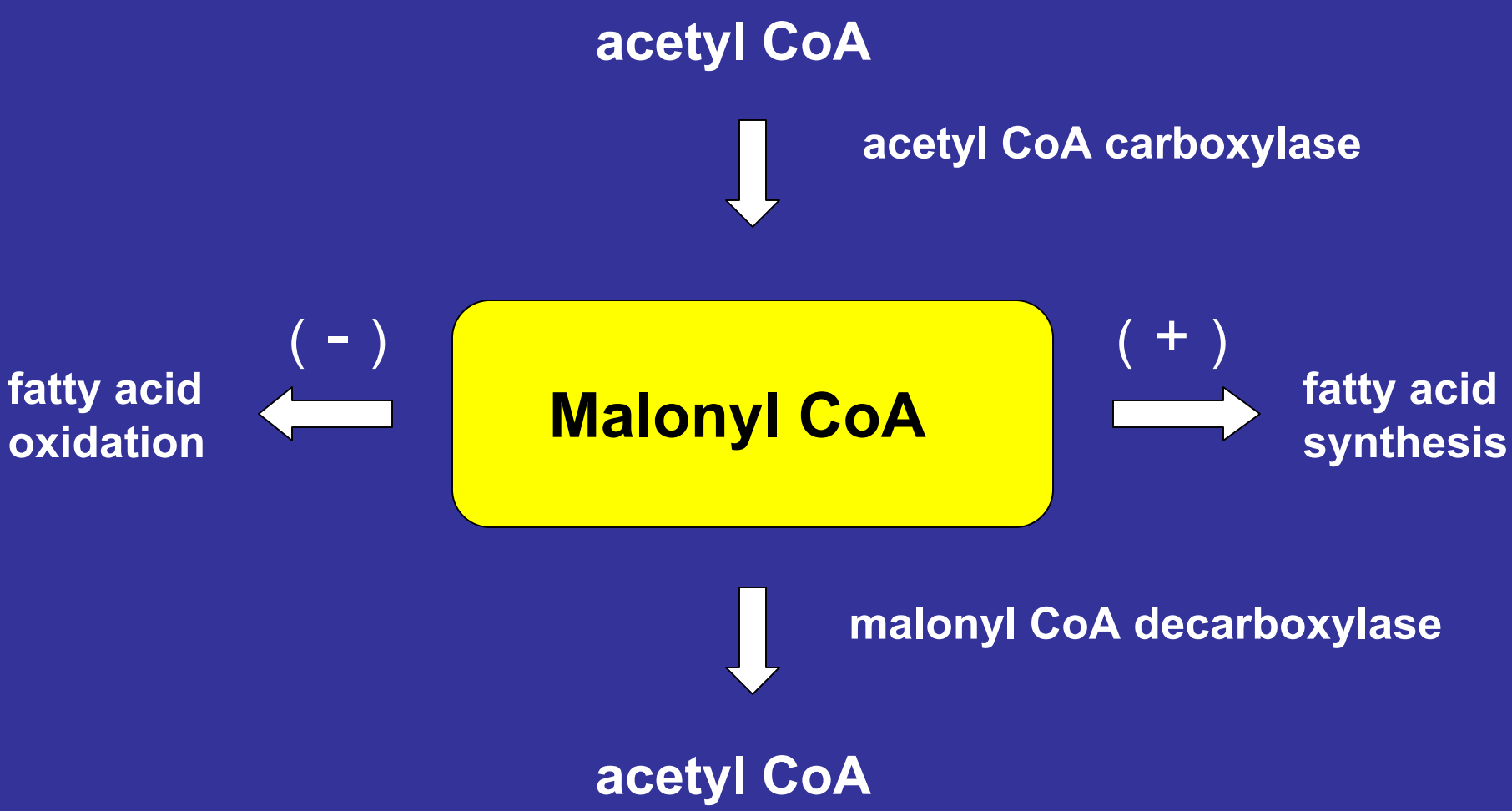
(+) Decanoylcarnitine (DC) and Fat Metabolism in Perfused Rat Liver

1 – ^{14}C oleic acid metabolism (30 minutes)
% recovered

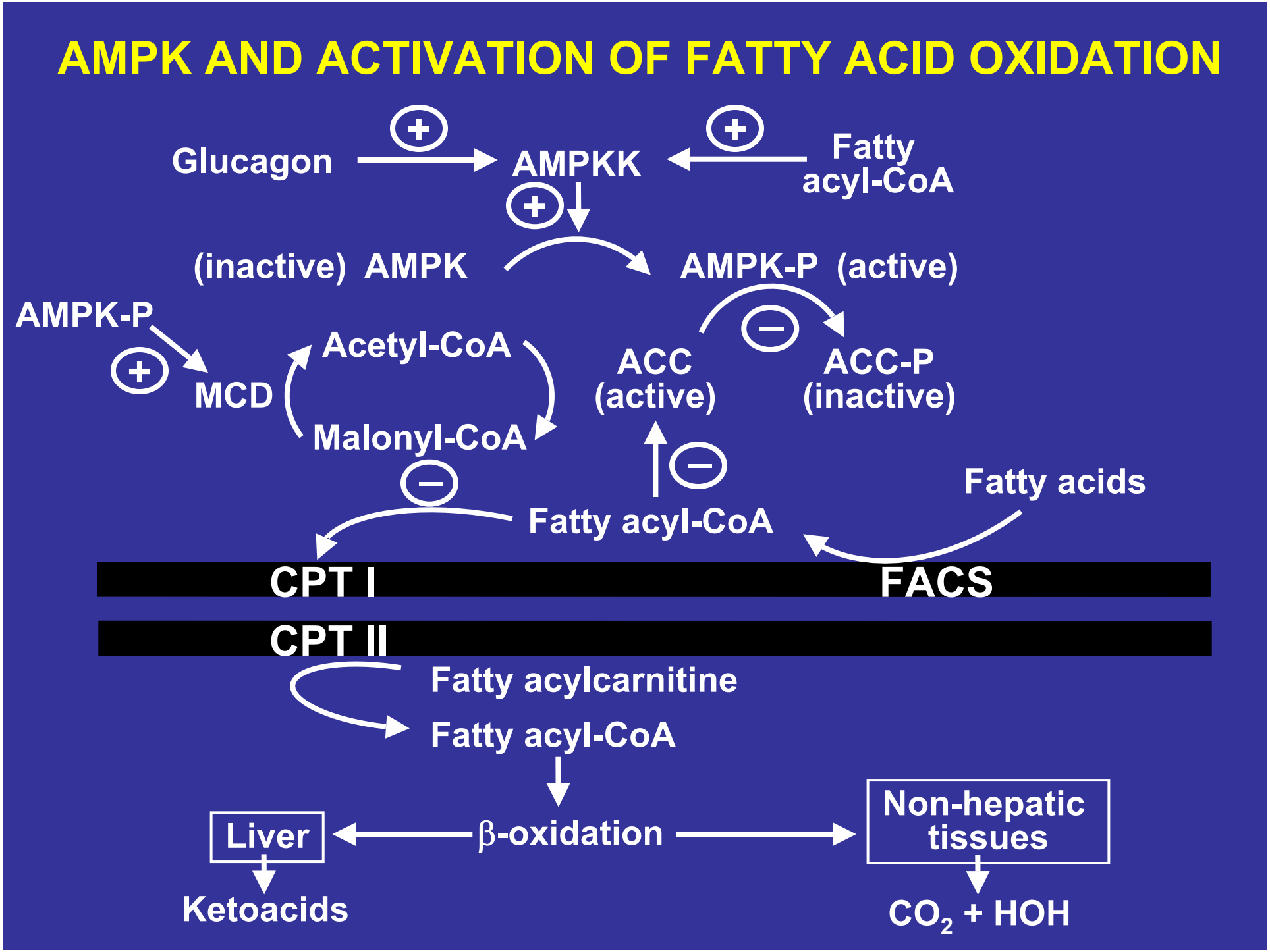
	Ketones	Liver Lipids	Total
Control	1.4	31.4	97.5
Fasted*	15.6	14.2	89.5
Fasted (+DC)*	0.9	27.9	92.5

*Fasted 24 hours

MALONYL CoA REGULATION



AMPK AND ACTIVATION OF FATTY ACID OXIDATION

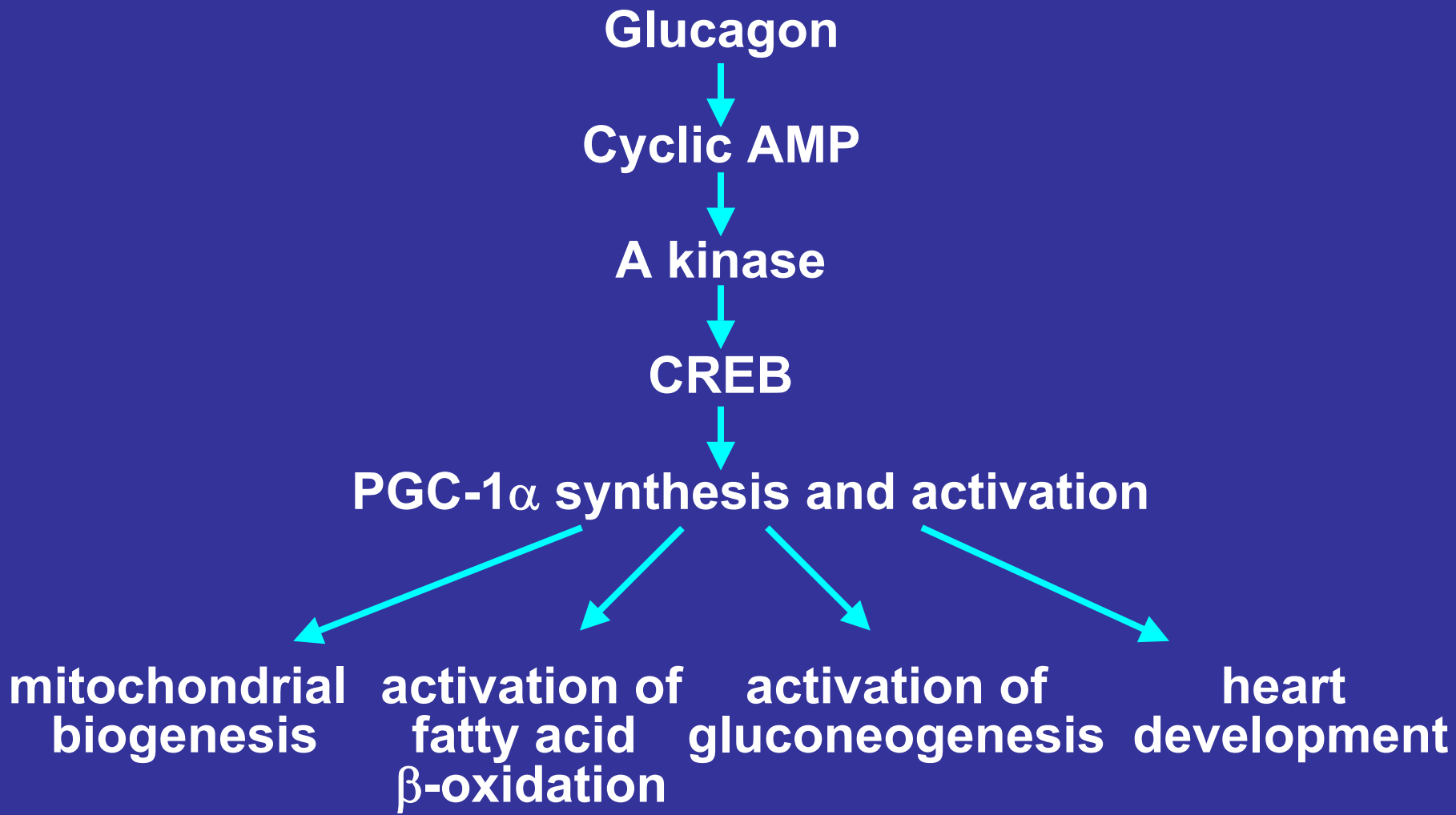


OTHER ACTIVATORS OF FATTY ACID β-OXIDATION

(1) Peroxisome proliferator-activated receptor-γ coactivator 1-α

(2) Stearoyl-CoA desaturase

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ COACTIVATOR 1 α (PGC-1α)



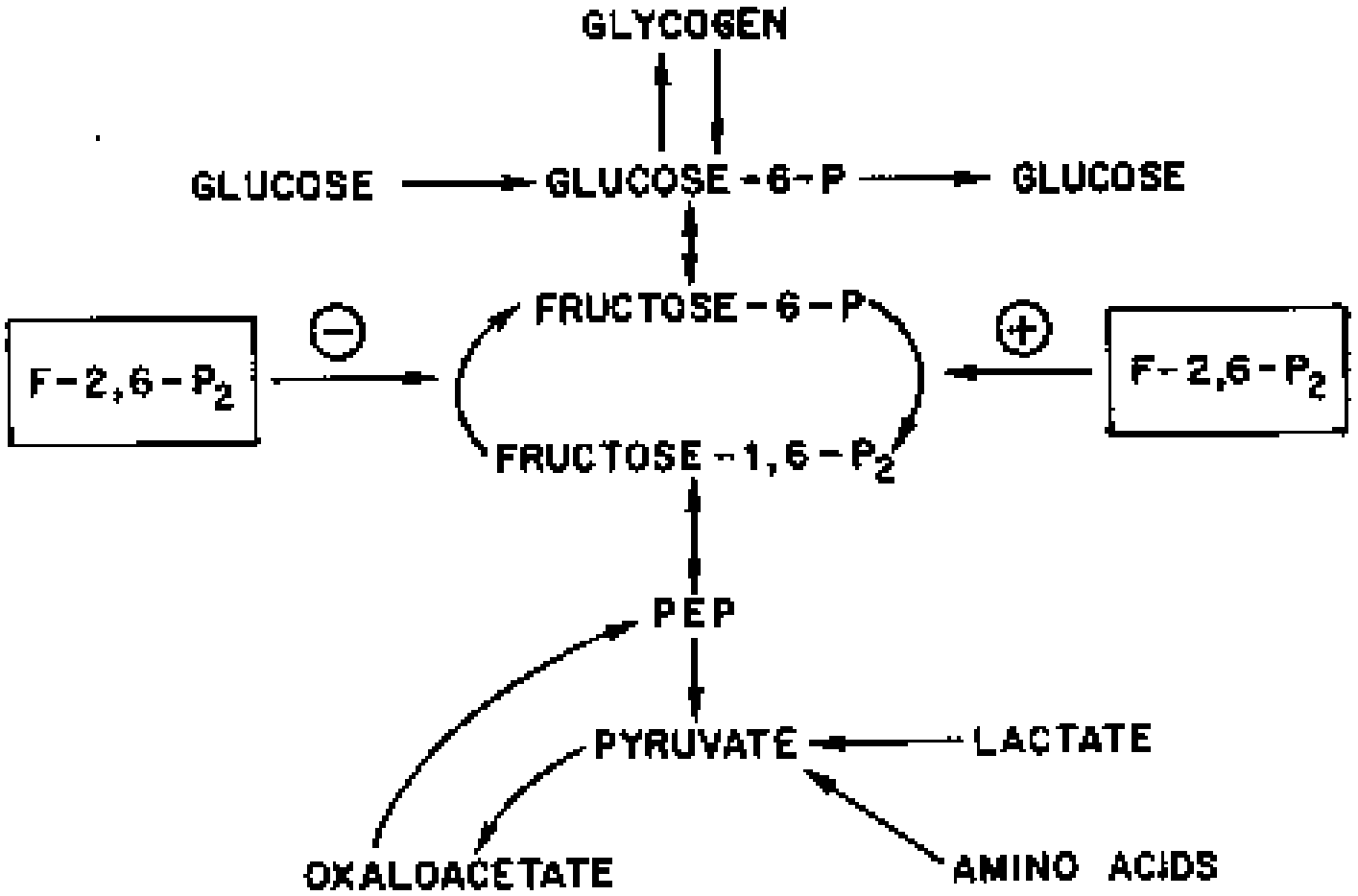
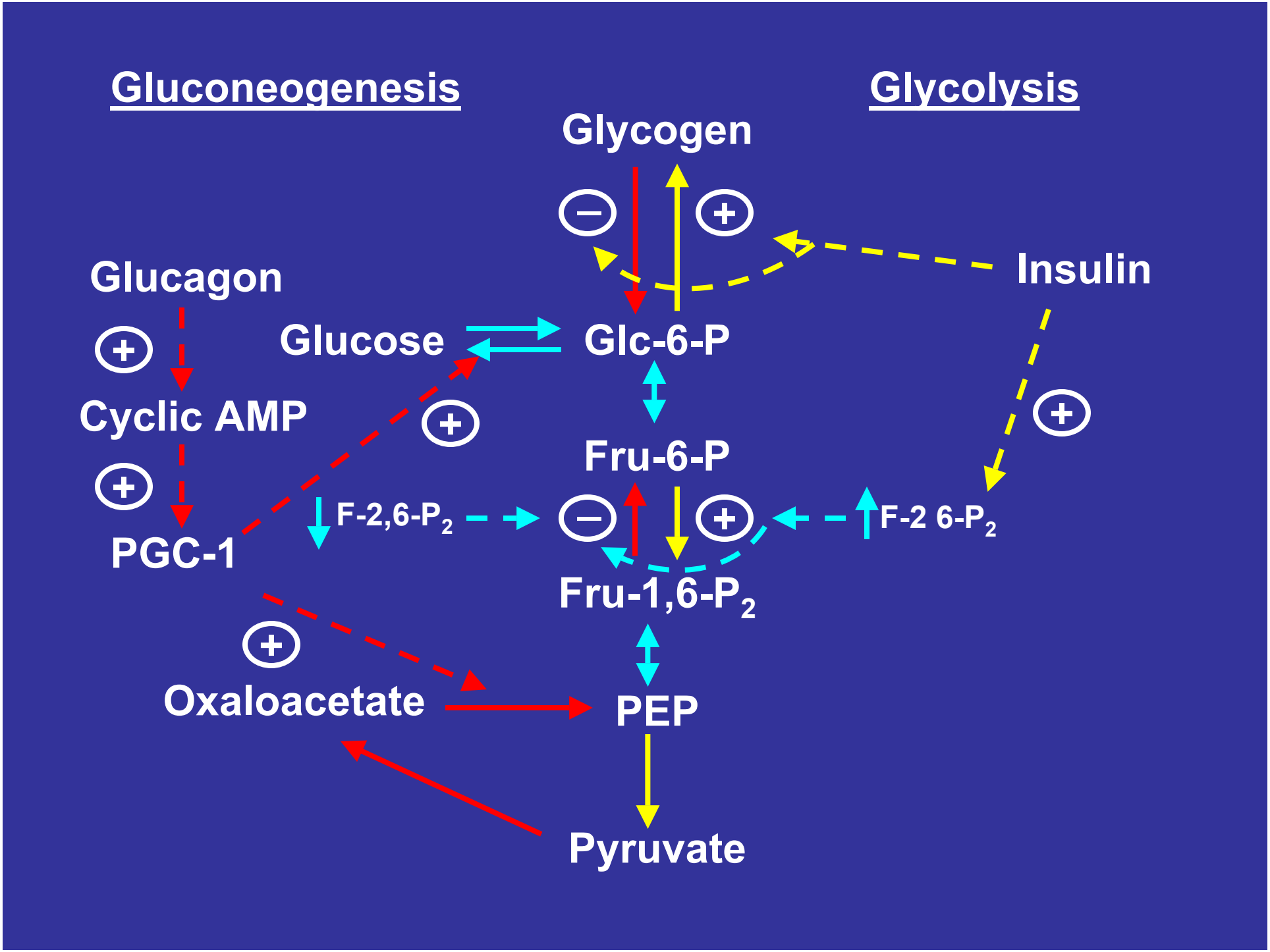
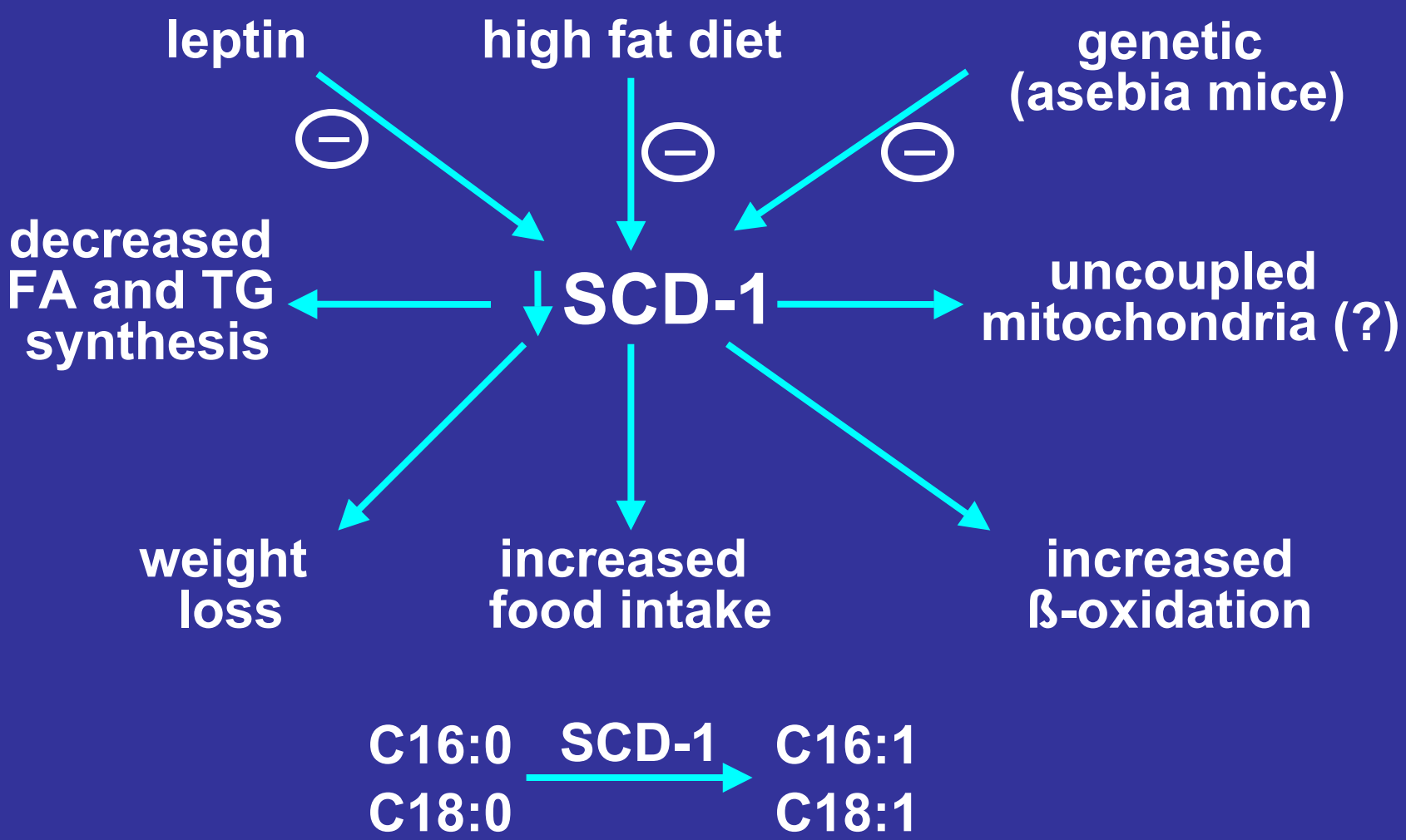


FIGURE 16. The regulation of glycolysis and gluconeogenesis by fructose-2,6-bisphosphate (F-2,6-P_2). F-2,6-P_2 activates phosphofructokinase, sustaining glycolysis, and deactivates fructose-1,6-bisphosphatase, inhibiting gluconeogenesis. See text for details. PEP stands for phosphoenolpyruvate.


Gluconeogenesis
Glycolysis
Glycogen
Glucagon
Insulin
Glucose
Glc-6-P
Cyclic AMP
Fru-6-P
PGC-1
F-2,6-P2
F-2 6-P2
Fru-1,6-P2
Oxaloacetate
PEP
Pyruvate

STEAROYL-CoA DESATURASE (SCD-1) DEFICIENCY



OTHER REGULATORS OF LIPOGENESIS

1. Insulin-induced gene 1 and 2 (Insig 1 and 2)
2. Carbohydrate-responsive element binding protein (ChREBP)

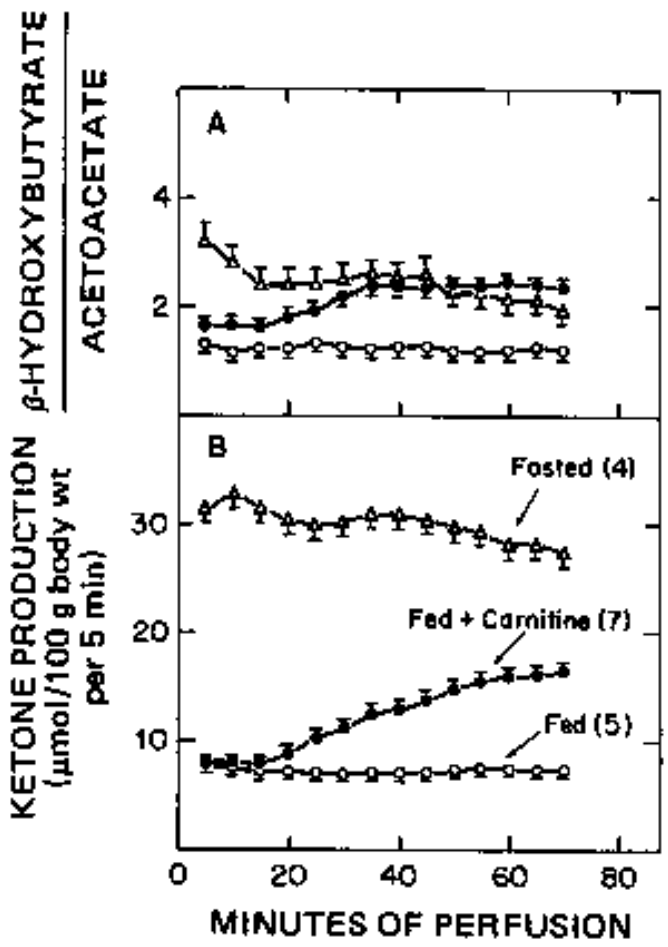


FIG. 2. Effect of carnitine on ketogenesis from oleic acid in perfused livers from fed rats. Livers were perfused with non-circulating medium containing 0.7 mM oleic acid and the output of acetoacetate and β-hydroxybutyrate was determined every 5 min. The symbols used in panels A and B are as follows: (○), livers from fed animals; (△), livers from fasted animals; (●), livers from fed animals in which L-carnitine was infused at a concentration of 0.5 mM from the 15-min time point. Values represent means ± SEM for the number of livers shown in parentheses.

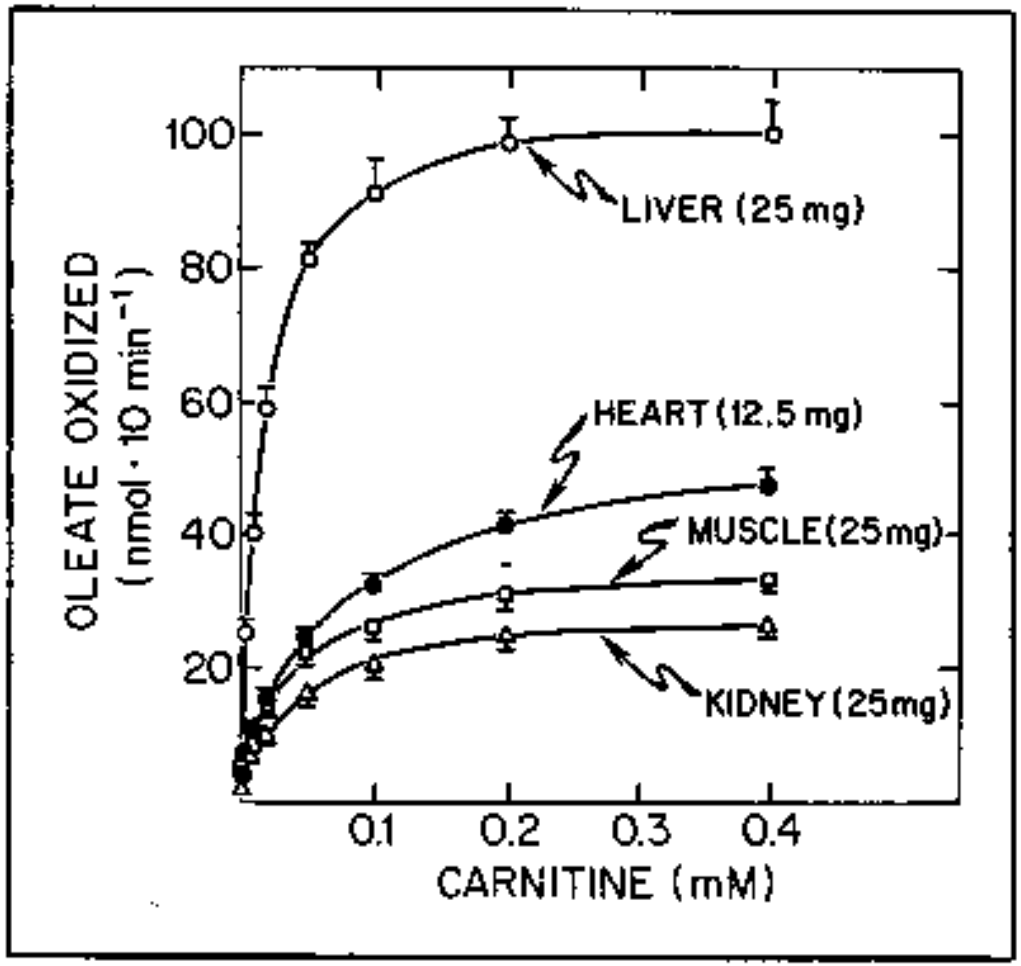
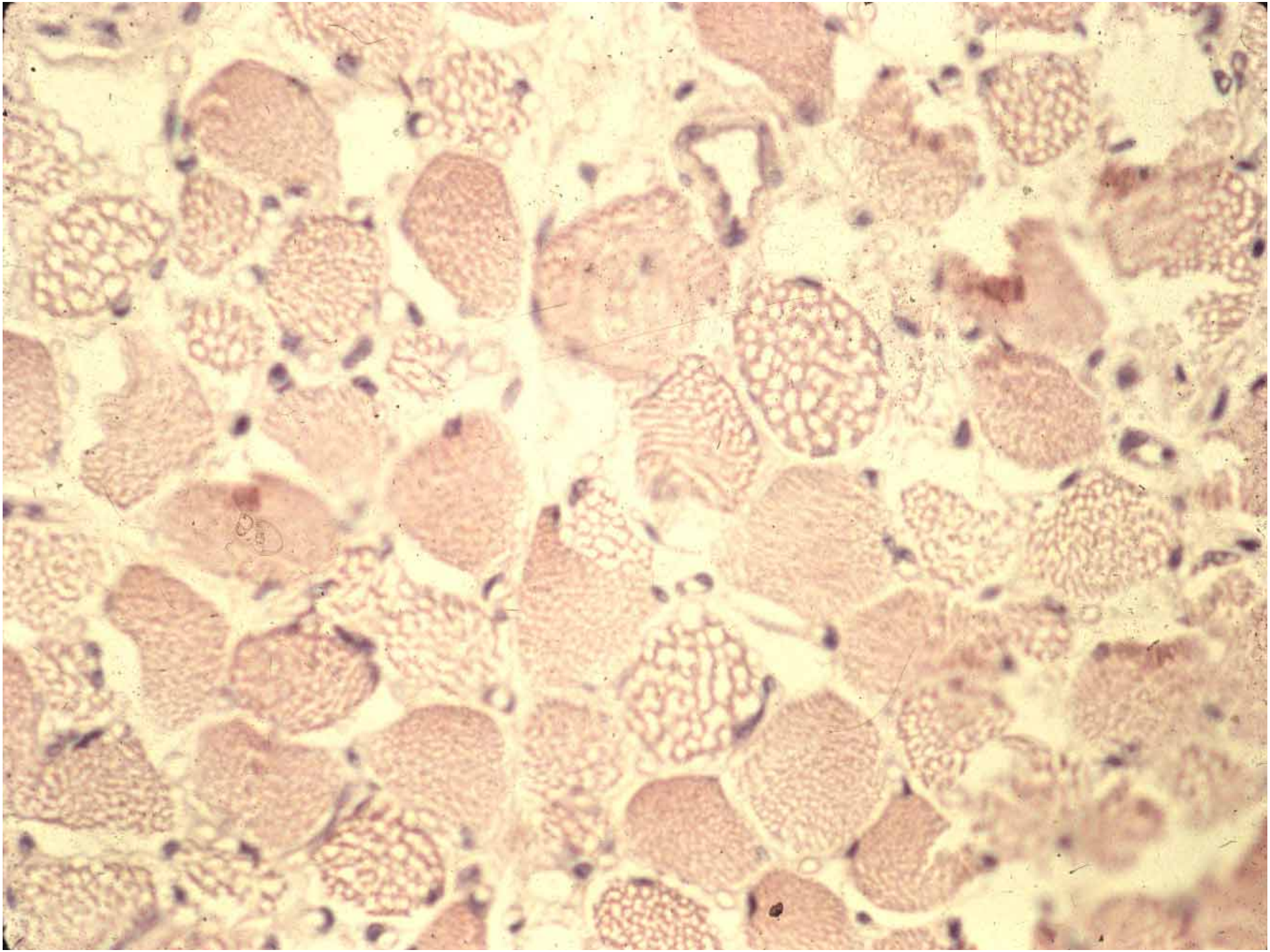


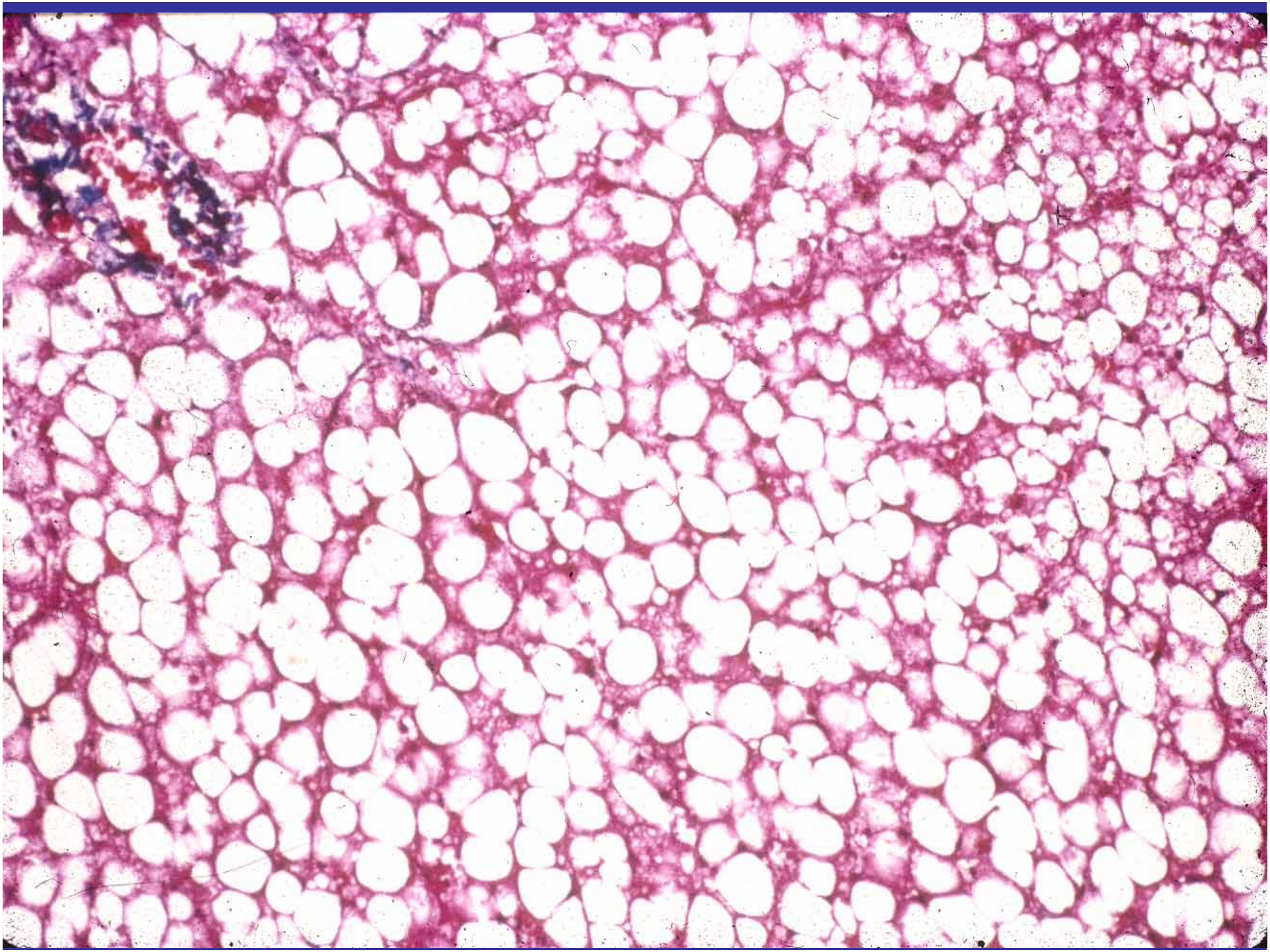
Figure 1. Relationship between the concentration of carnitine and the rate of oleate oxidation in homogenates of rat tissues. The indicated quantities of tissue were incubated as described under "Methods." Values are means ± SEM for three experiments with each tissue.

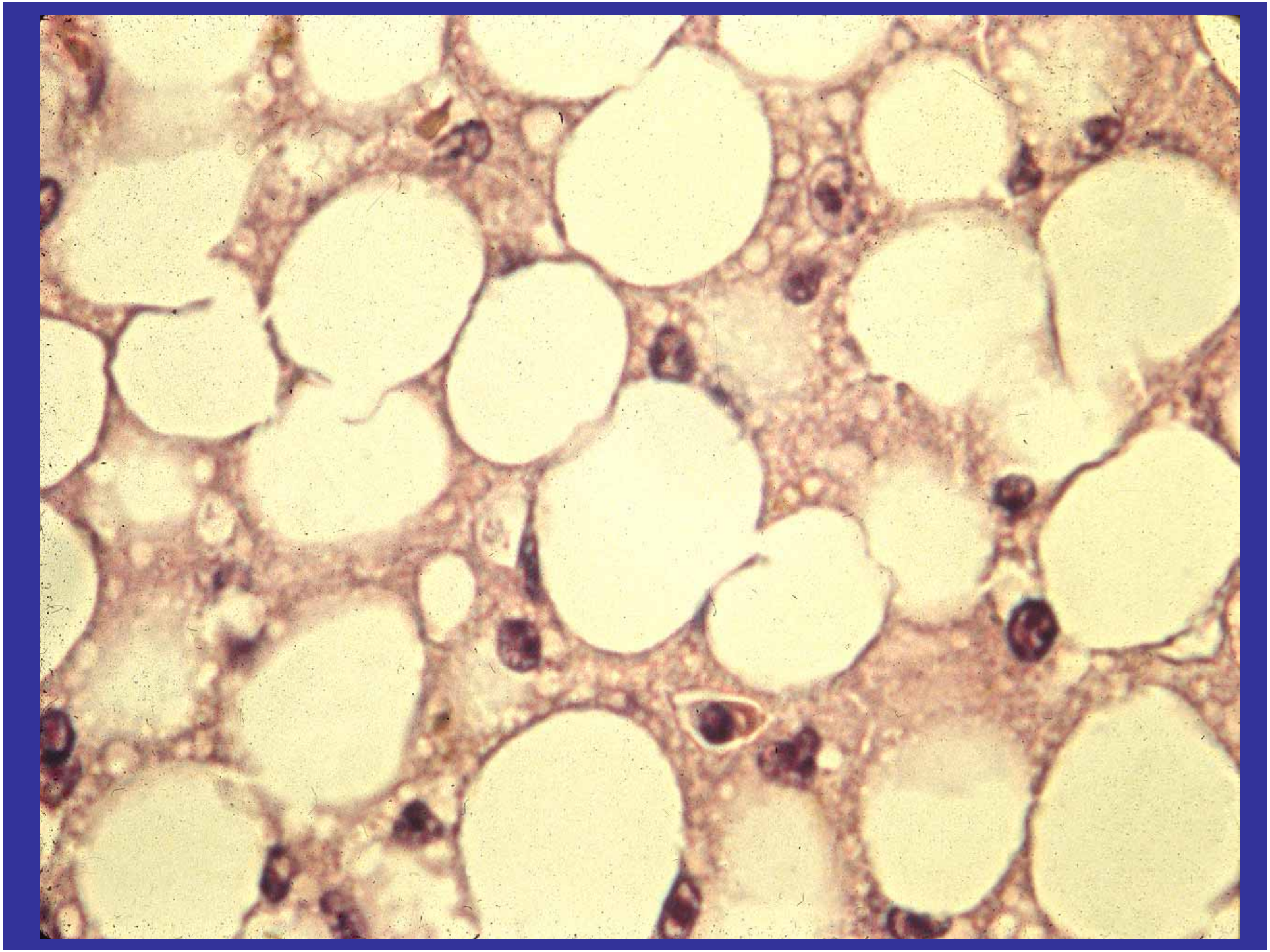
Treatment	Ketone production from oleate, μmol/100 g body wt per 30 min	Free carnitine	Total carnitine
		nmol/g wet wt of liver	
Fed (8)	26 ± 3	40 ± 5	102 ± 10
Fed, glucagon 3 hr (6)	87 ± 5	68 ± 8	220 ± 13
Fasted (6)	118 ± 8	70 ± 5	228 ± 13
Alloxan diabetic (6)	192 ± 10	172 ± 12	416 ± 6

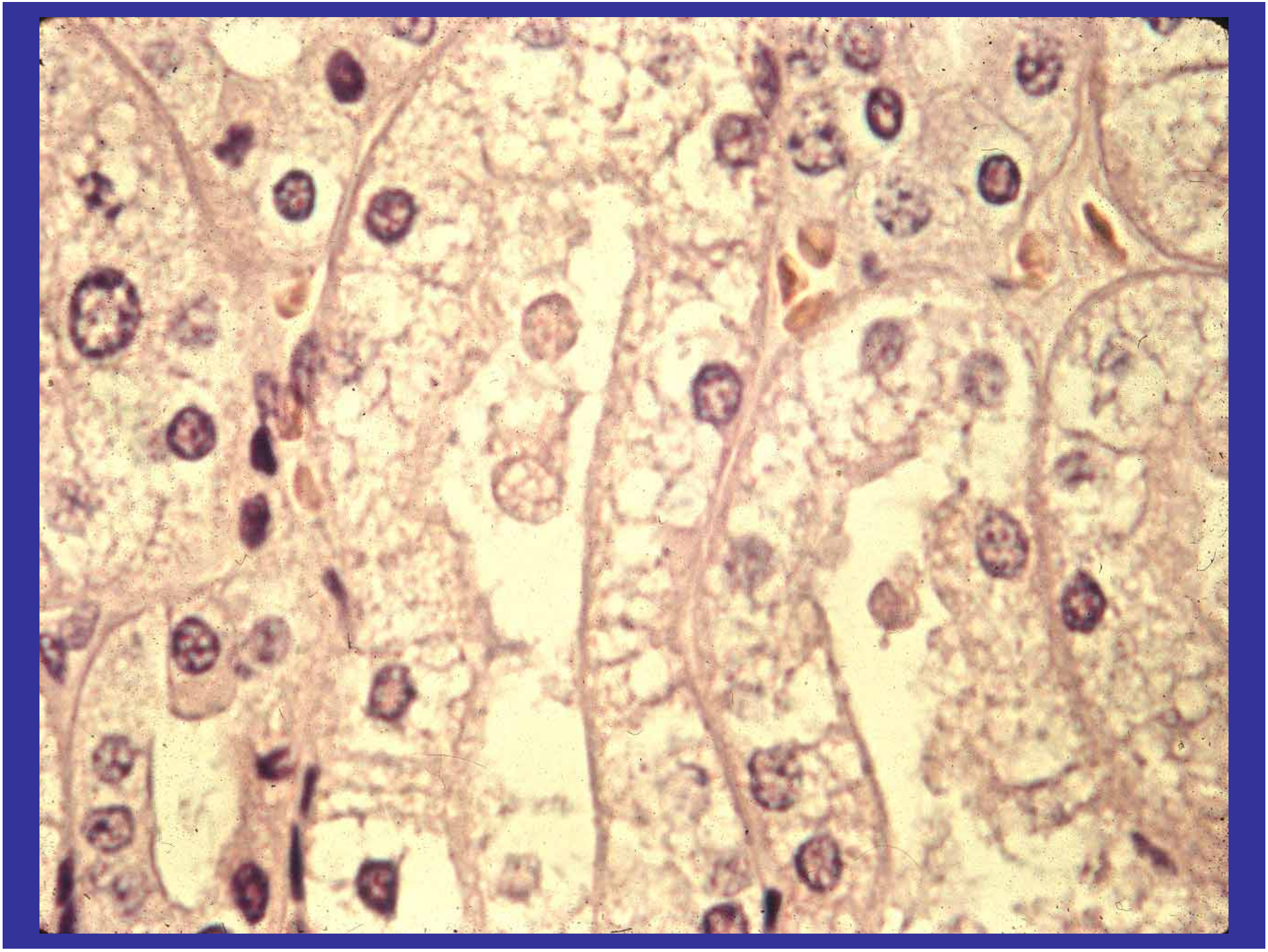
FUNDAMENTAL THESES

1. If too little fat is oxidized, life is threatened.
2. If too much fat is oxidized, life is threatened.









SYSTEMIC CARNITINE DEFICIENCY

1. Fasting hypoglycemia
2. No or limited fasting ketosis
3. Elevated plasma NH_3
4. Hepatic encephalopathy with “flap” and seizures
5. Multiorgan triglyceride storage
6. Muscle weakness and rhabdomyolysis
7. Progressive cardiomyopathy
8. Carnitine low in plasma and tissues
9. Gene defect: mutated carnitine transporter ($OCTN_2$)

CEREBRAL THROMBOSIS IN DKA

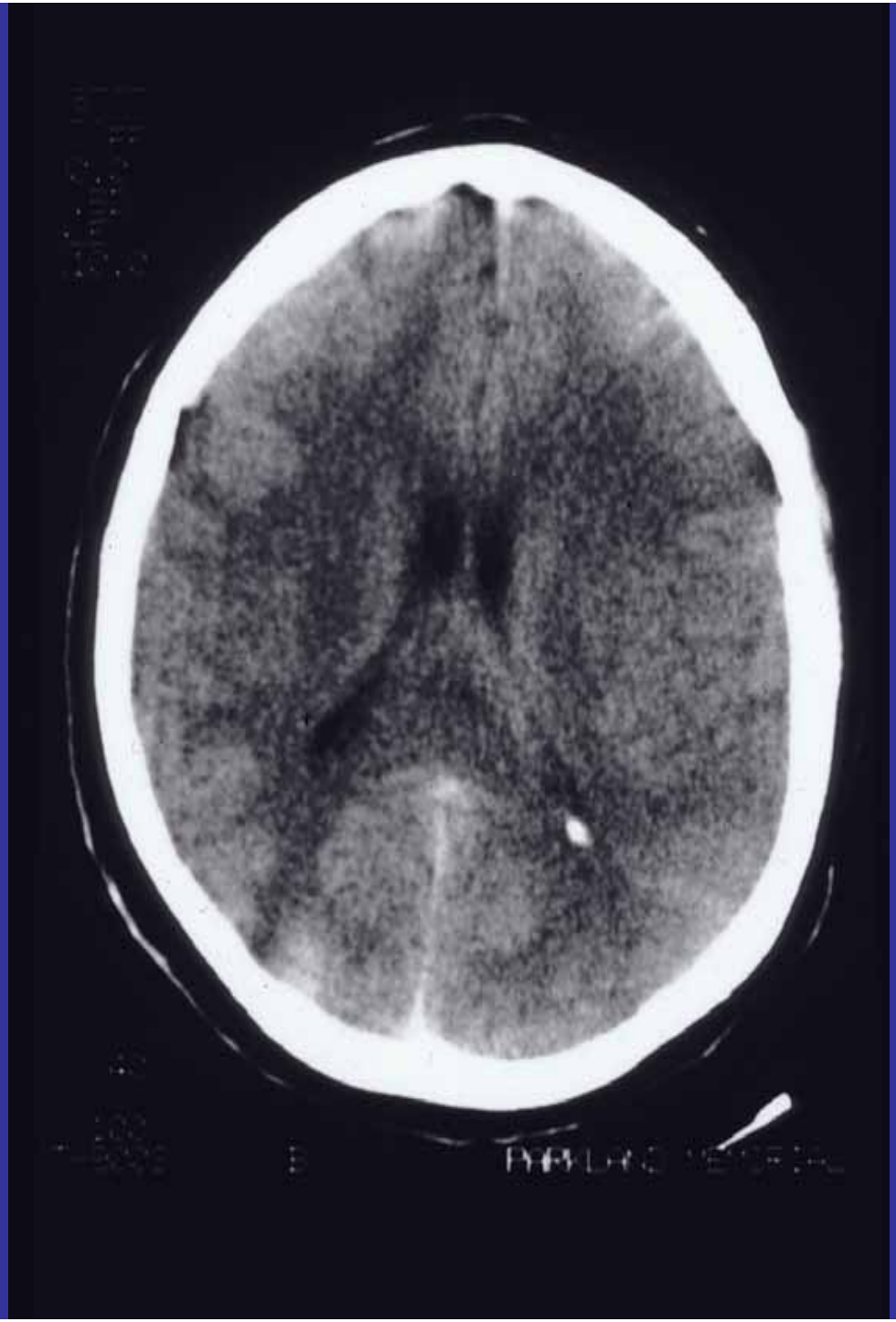
W.G., a 21 y/o BM with known insulin-dependent diabetes mellitus, was admitted in diabetic ketoacidosis. Admission hemoglobin 20.3 g/dl, hematocrit 60.8%, WBC 21,200. Ethanol negative. Trace salicylate. Lactate 2.0 mM, amylase 182 (nl <110), lipase 798 (nl <208), pH 7.15, pO_2 99 mm.

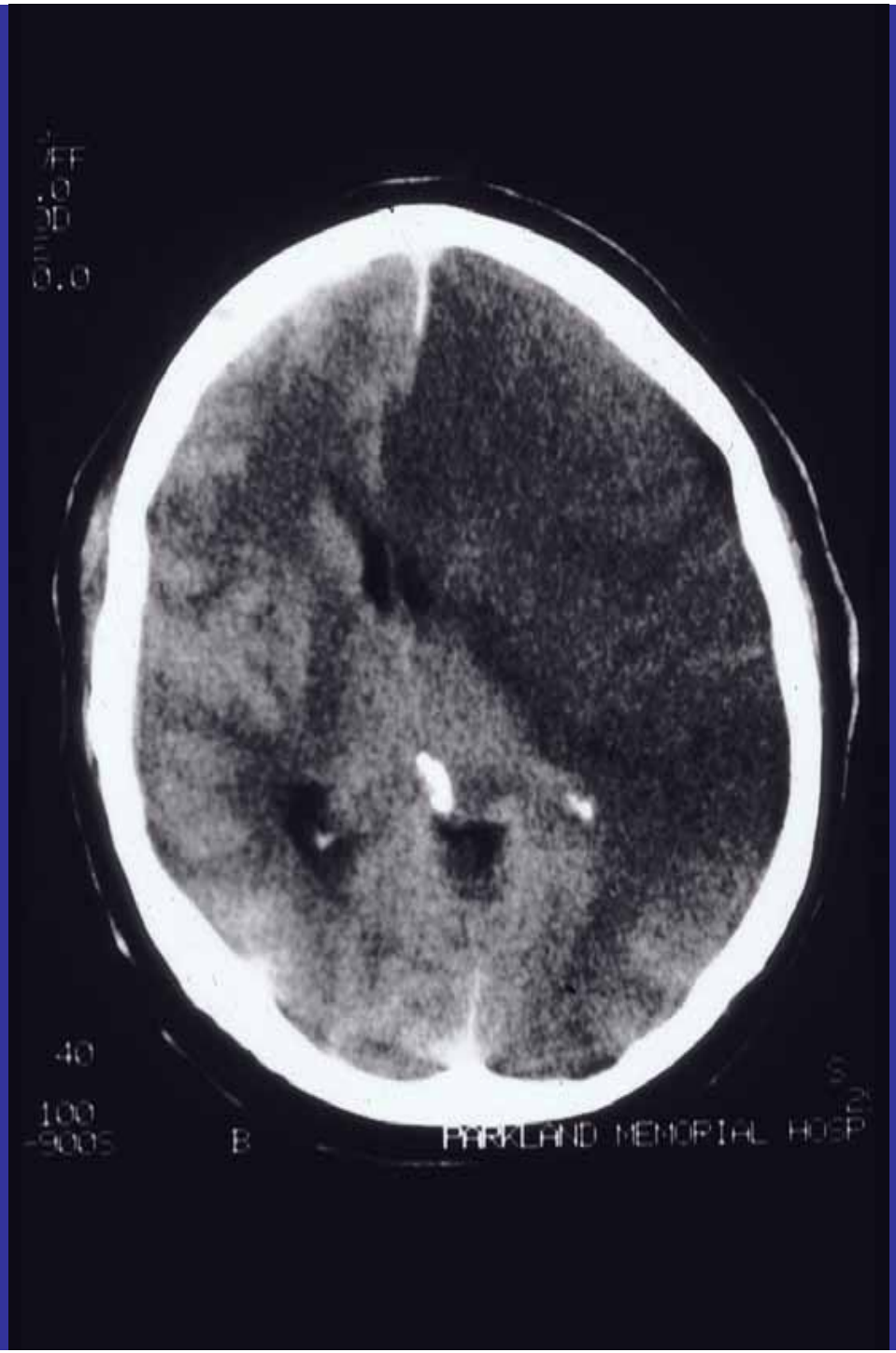
CEREBRAL THROMBOSIS IN DKA

Time	Glucose	Na	K	HCO_3	Cl	Creat	Gap	State
2130	1457	140	6.5	8	96	6.2	36	Drowsy
0130	554	158	2.9	17	128	4.1	13	Drowsy
0800	295	145	3.9	18	115	2.6	12	Drowsy

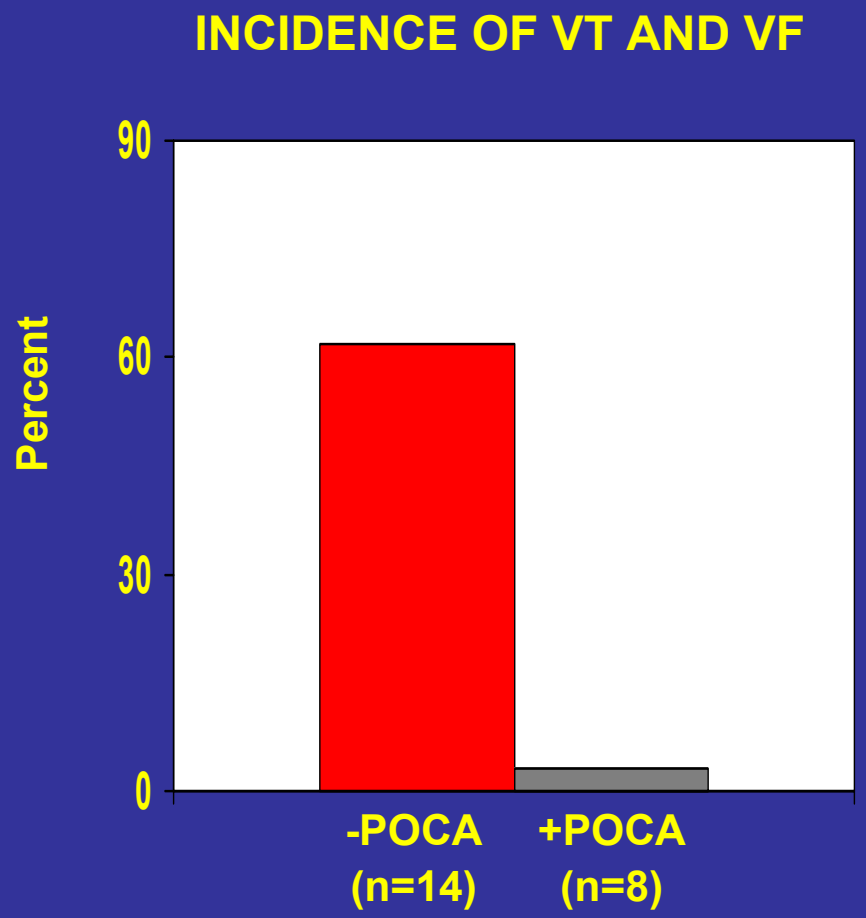
1130 Unresponsive. Right facial paralysis, right hemiparesis. Head CT negative. Spinal tap unremarkable.

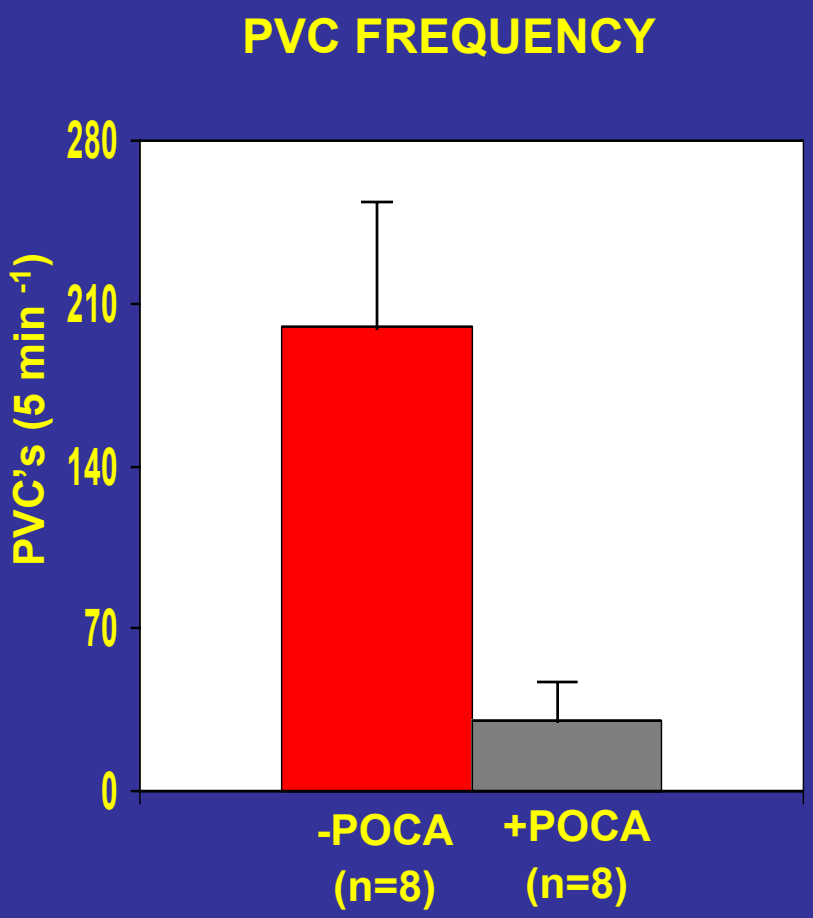
Next day - Left hemiparesis, dilated right pupil. CT-stroke, edema, shift. Died 72 hours after admission.




0.0
40
100
B
PARKLAND MEMORIAL HOSP

ACUTE CORONARY OCCLUSION





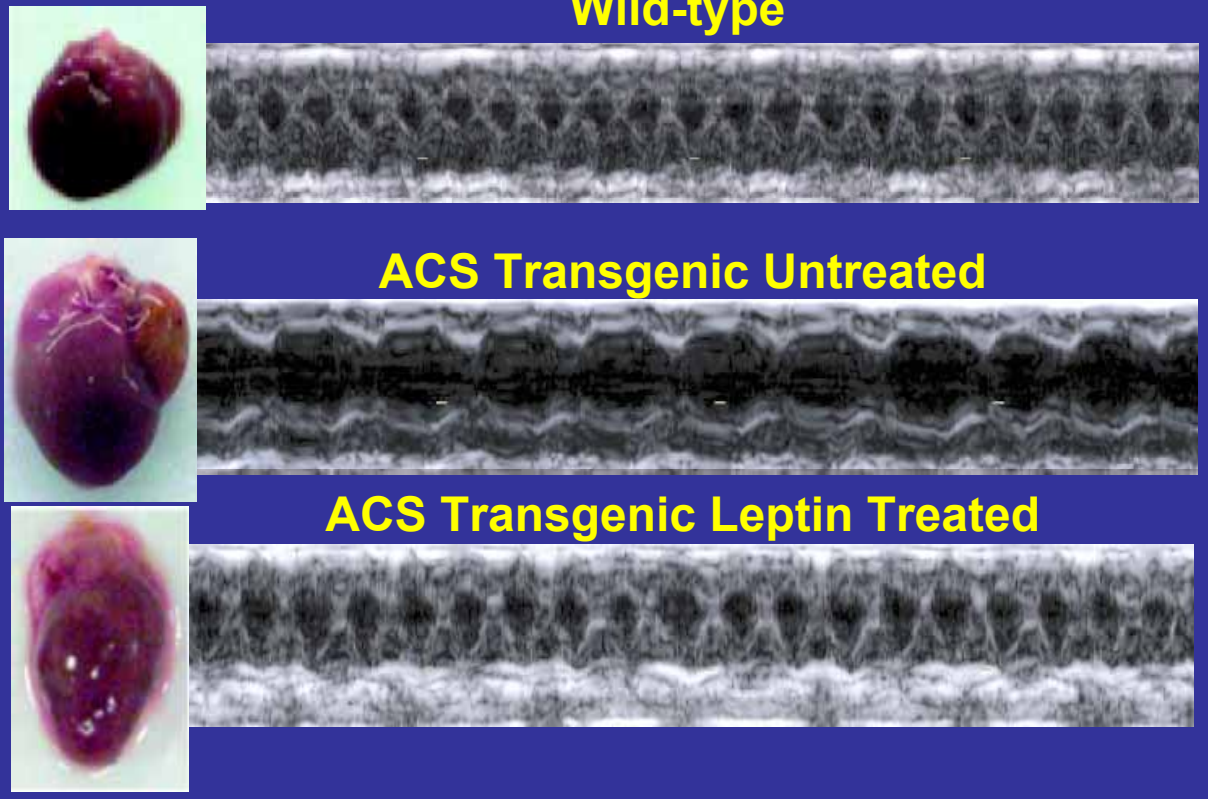
From Corr PB, *et al.* J. Clin. Invest. 1989, 83: 927-936.

FAT OXIDATION/CPT SYSTEM

1. Diabetic ketoacidosis
2. Hypoglycemia/Reye syndrome
3. Insulin secretion
4. Insulin resistance/pathogenesis of NIDDM
5. Primary muscle disease
6. Sudden death in coronary artery disease
7. Control of feeding signals in hypothalamus
8. Sperm development and motility
9. Therapy of obesity

METABOLIC FUTURE FOR THE CARNITINE /CPT SYSTEM

1. Treatment of non-alcoholic steatohepatitis
2. Treatment of lipotoxicity in heart
3. Treatment of type 2 diabetes mellitus and insulin resistance
4. Treatment of obesity


Wild-type
ACS Transgenic Untreated
ACS Transgenic Leptin Treated
Heart TG (mg/g)
3.0
1.5
0
Wild-type
ACS Transgenic Untreated
ACS Transgenic Leptin Treated