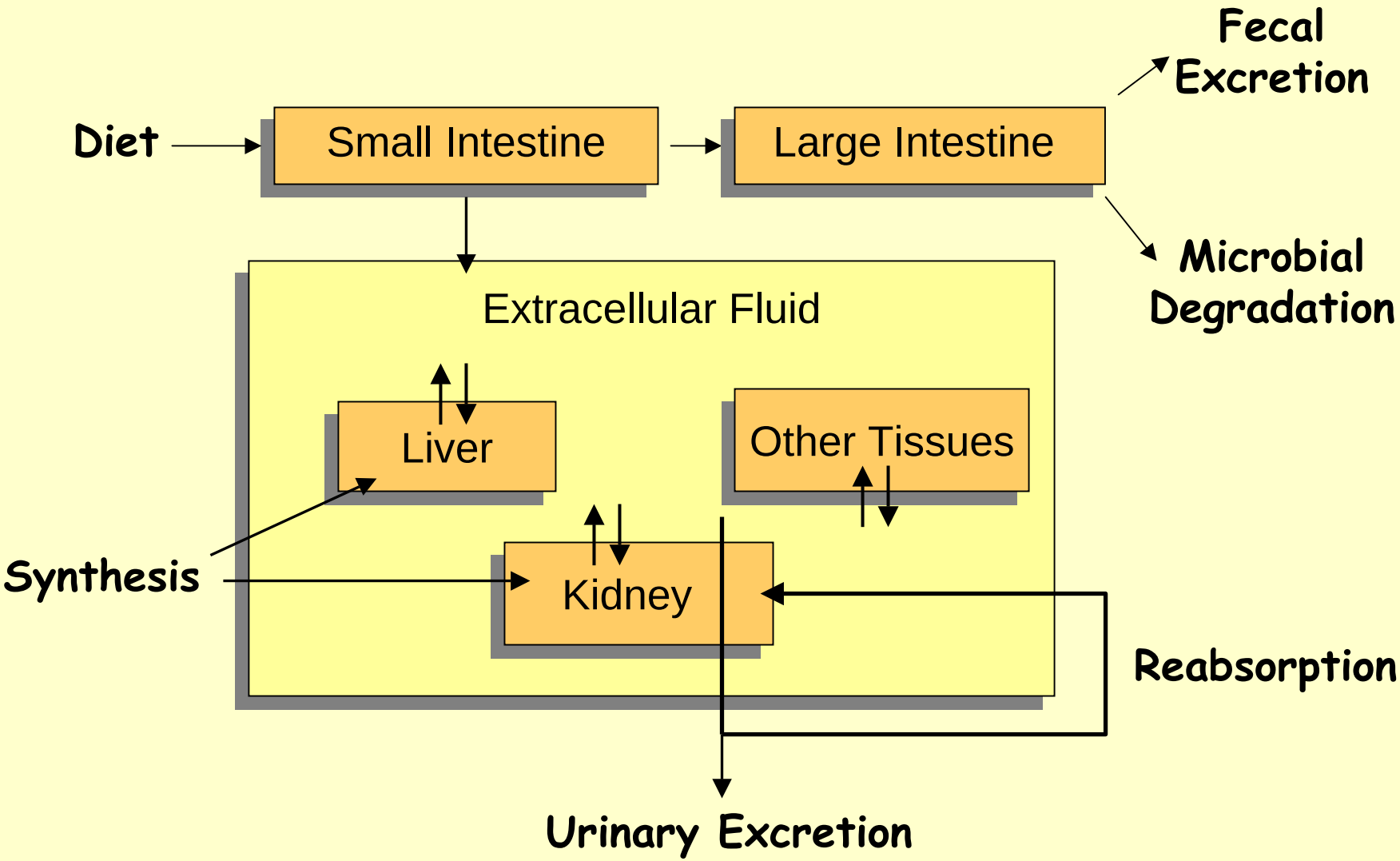
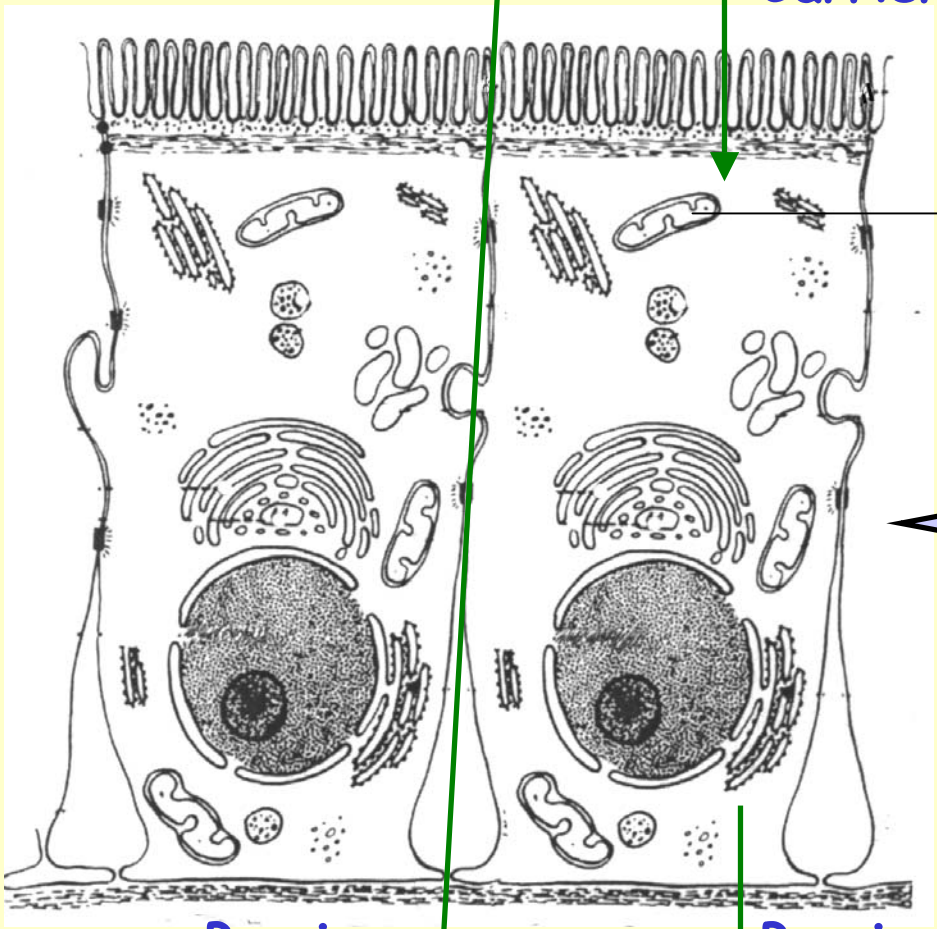
Kinetics, Pharmacokinetics, and Regulation of L-Carnitine and Acetyl-L-carnitine Metabolism

Charles J. Rebouche, Ph.D.

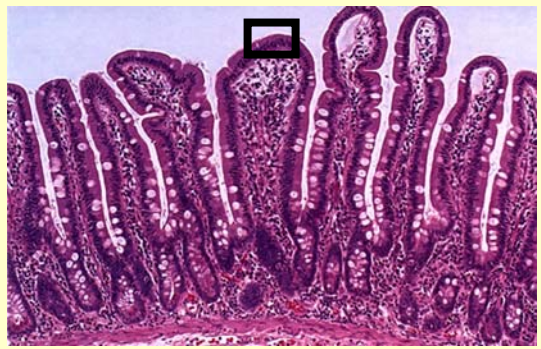

Fecal
Excretion
Diet
Small Intestine
Large Intestine
Microbial
Degradation
Extracellular Fluid
Liver
Other Tissues
Synthesis
Kidney
Reabsorption
Urinary Excretion

Carrier-mediated and Passive



Carnitine + Acetyl-CoA

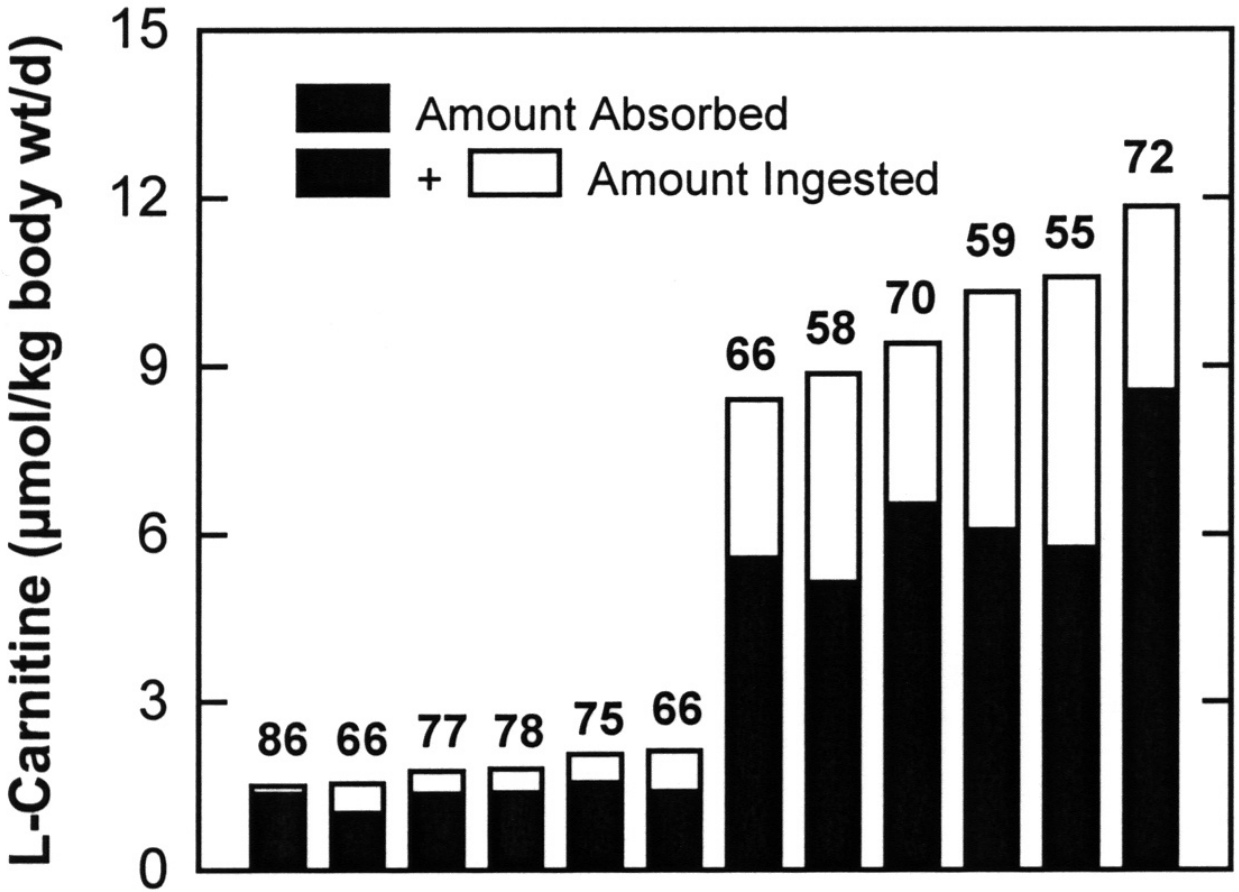
Acetylcarnitine + CoA



Passive
Paracellular

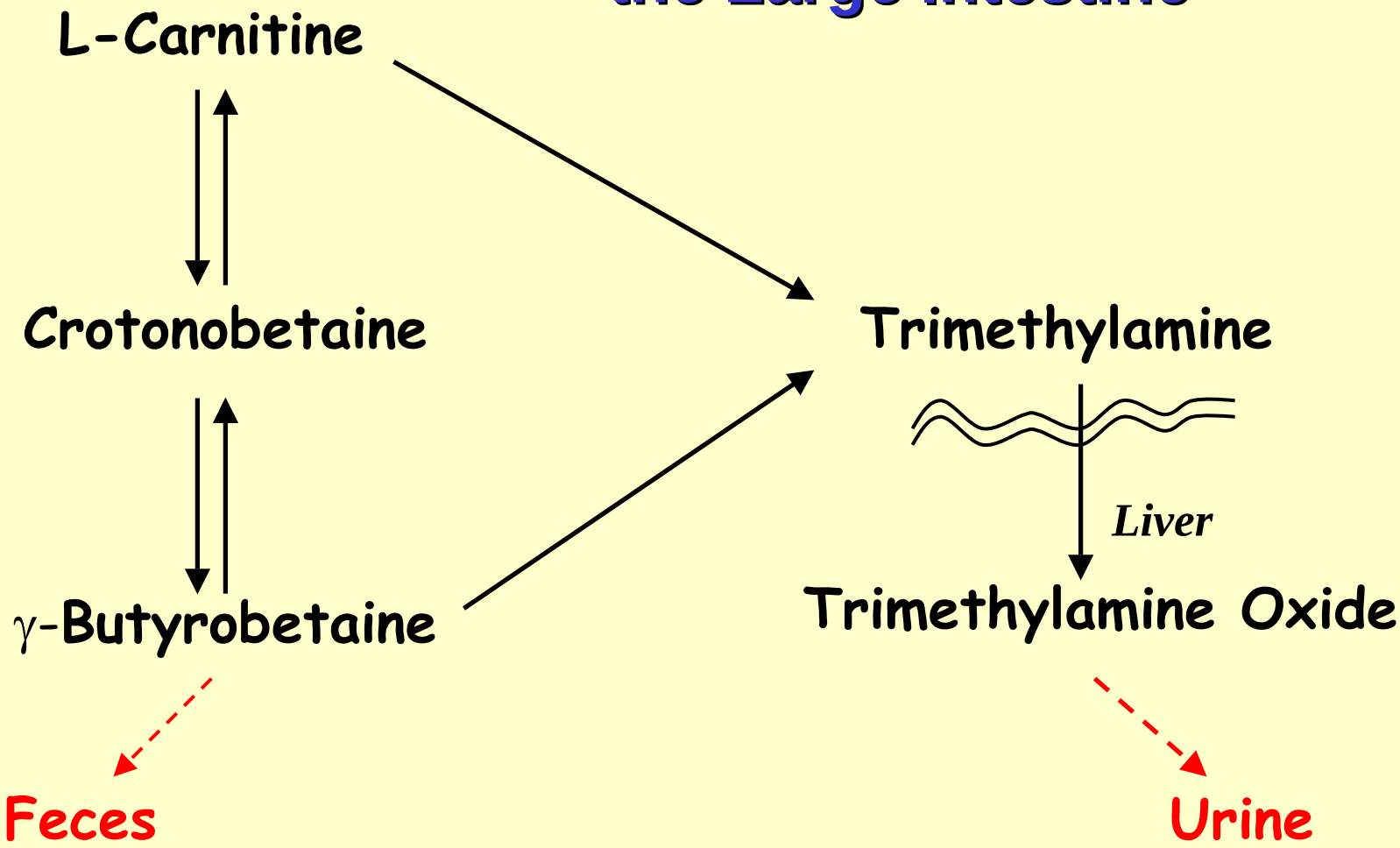
Passive
Transcellular

Absorption of Dietary L-Carnitine

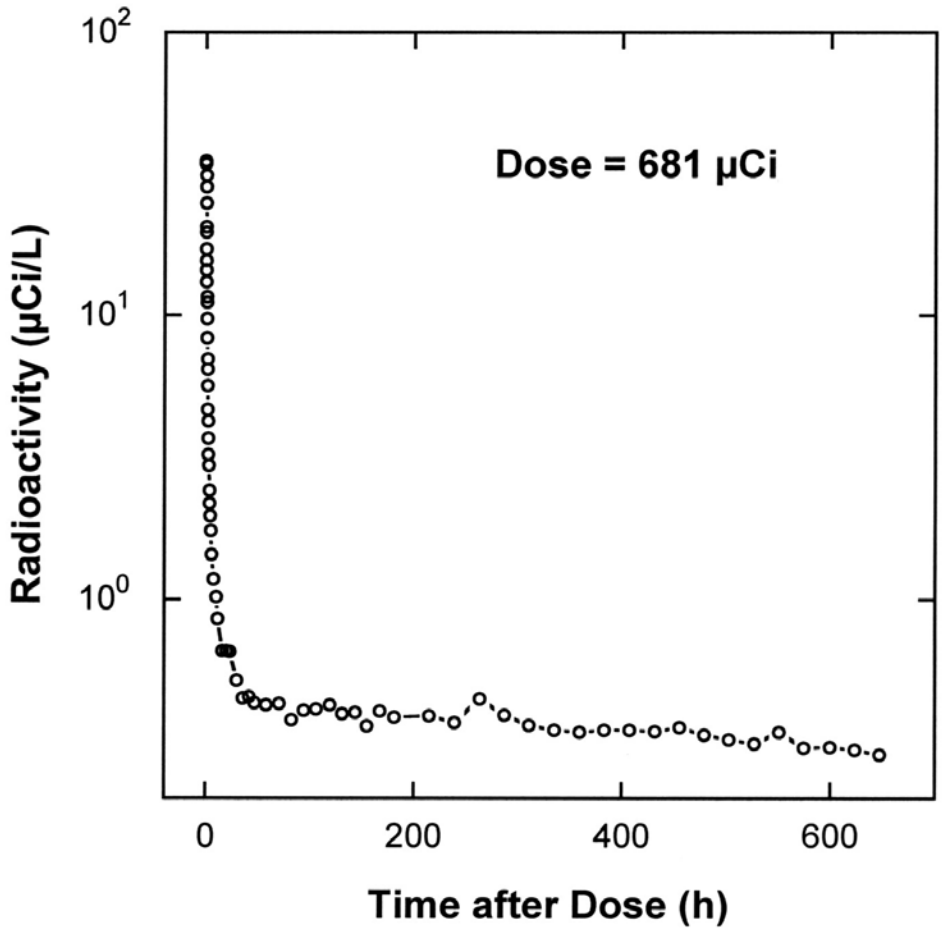


Data from: Rebouche & Chenard (1991) J Nutr 121:539-546

Metabolism of L-Carnitine in the Large Intestine

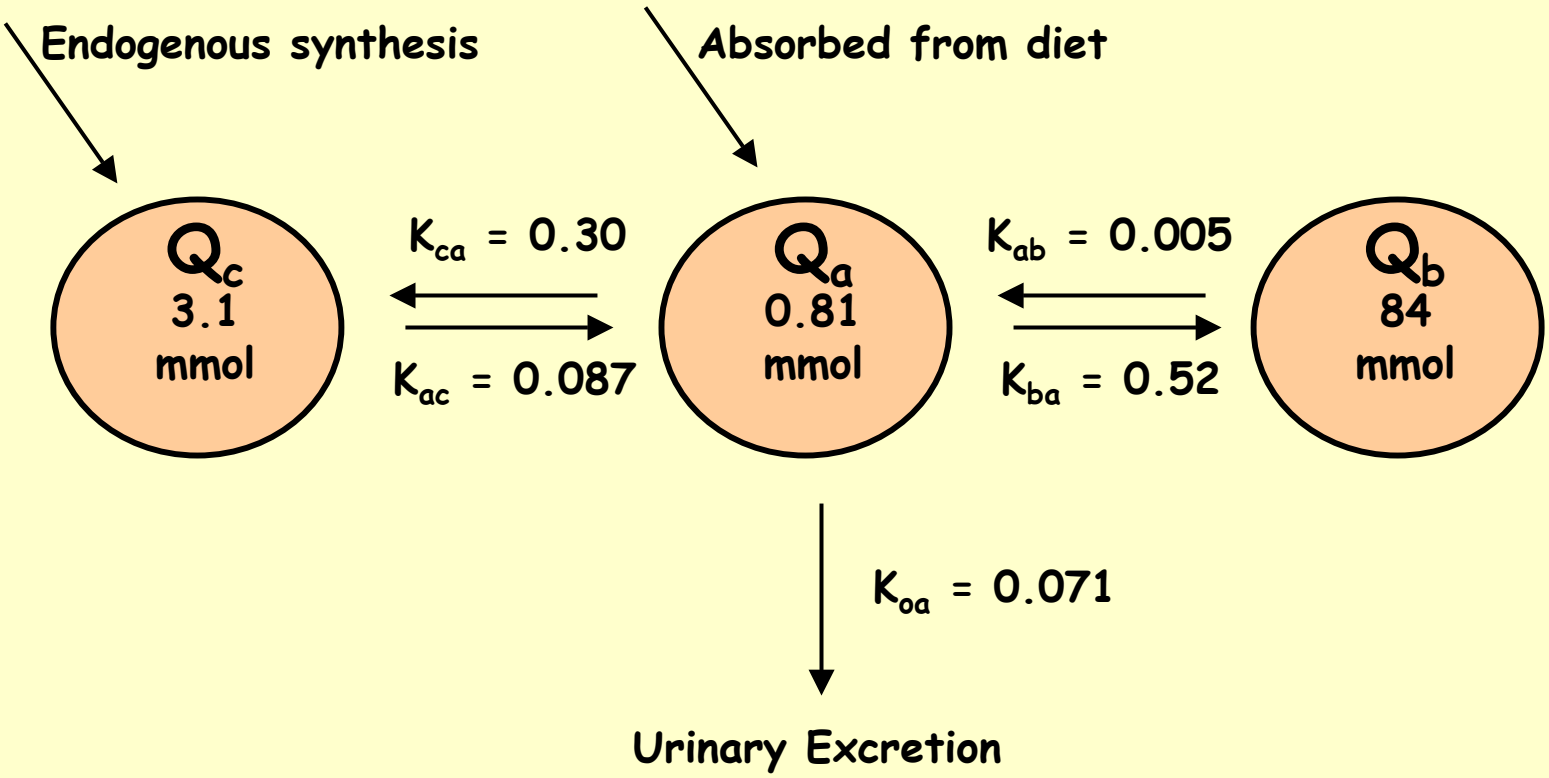


Carnitine Kinetics in Humans



Data from: Rebouche & Engel (1984) J Clin Invest 73, 857-867

A Kinetic Model for Carnitine Metabolism in Humans



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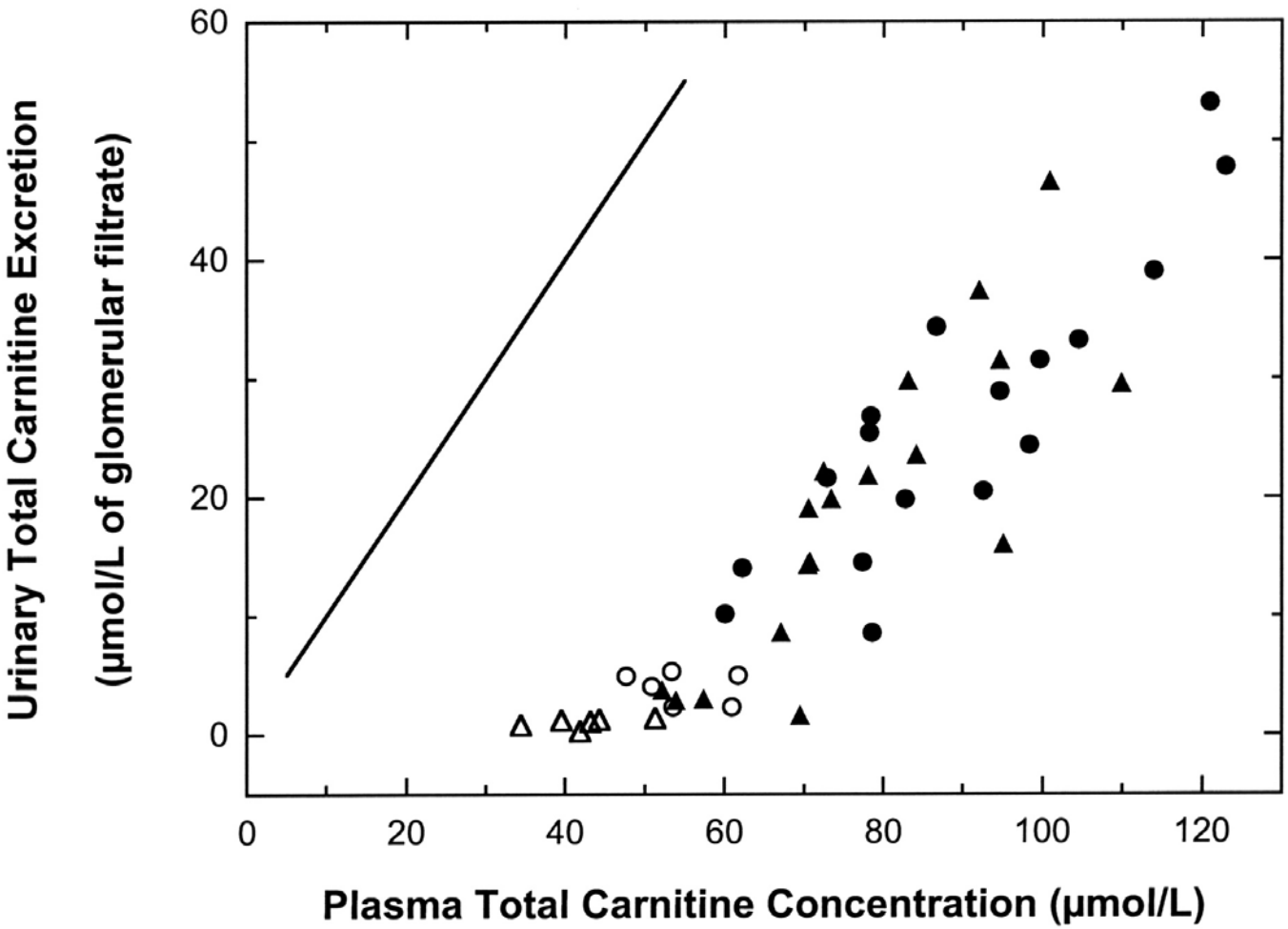
Renal Carnitine Excretion



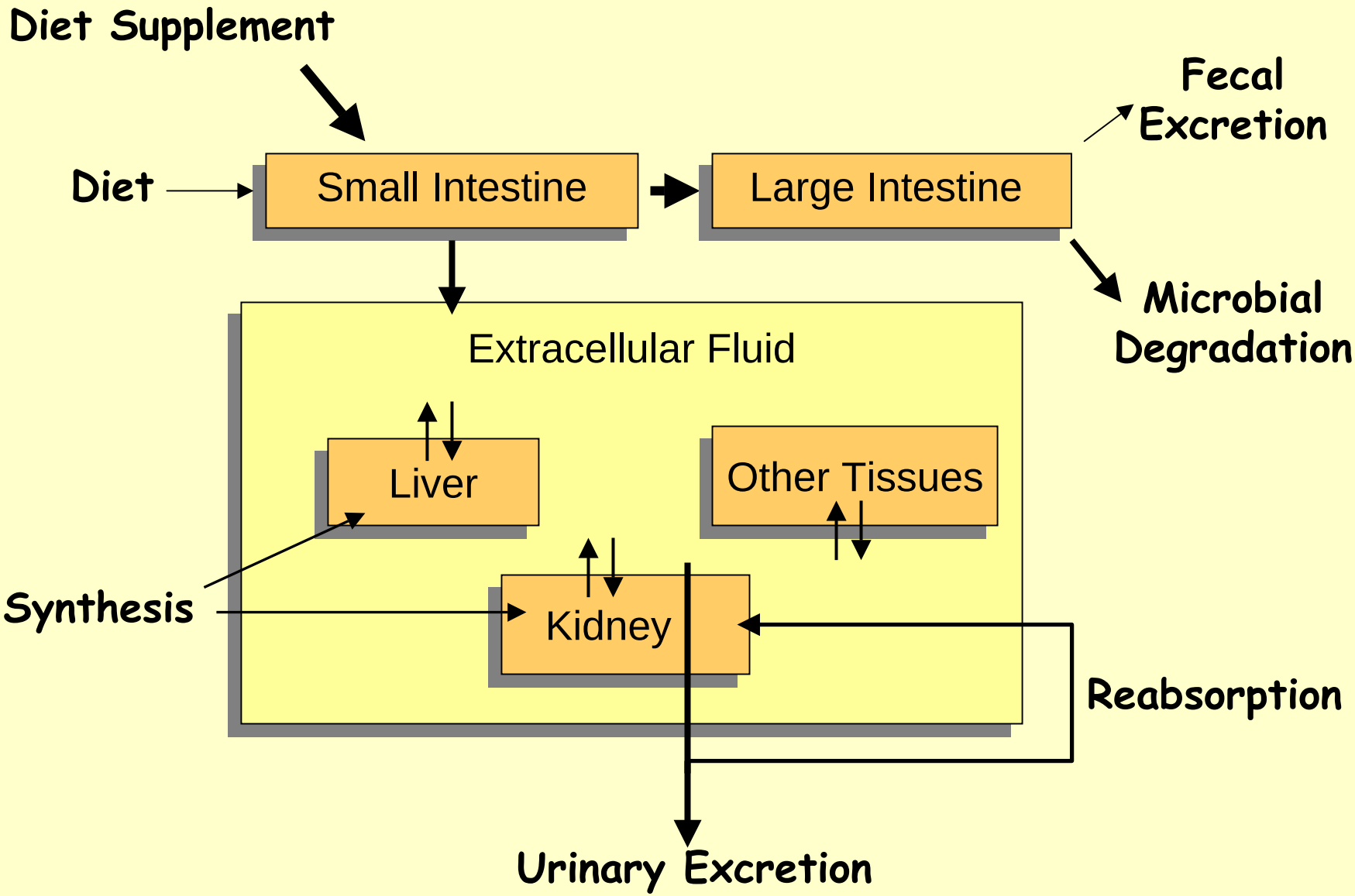
Open symbols: baseline; no infusion

Closed symbols: carnitine infusion

Circles: omnivores

Triangles: vegans

Data from: Rebouche, et al. (1993) Am J Clin Nutr 58:660-665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Small Intestine
Large Intestine
Fecal Excretion
Microbial Degradation
Extracellular Fluid
Liver
Other Tissues
Synthesis
Kidney
Reabsorption
Urinary Excretion

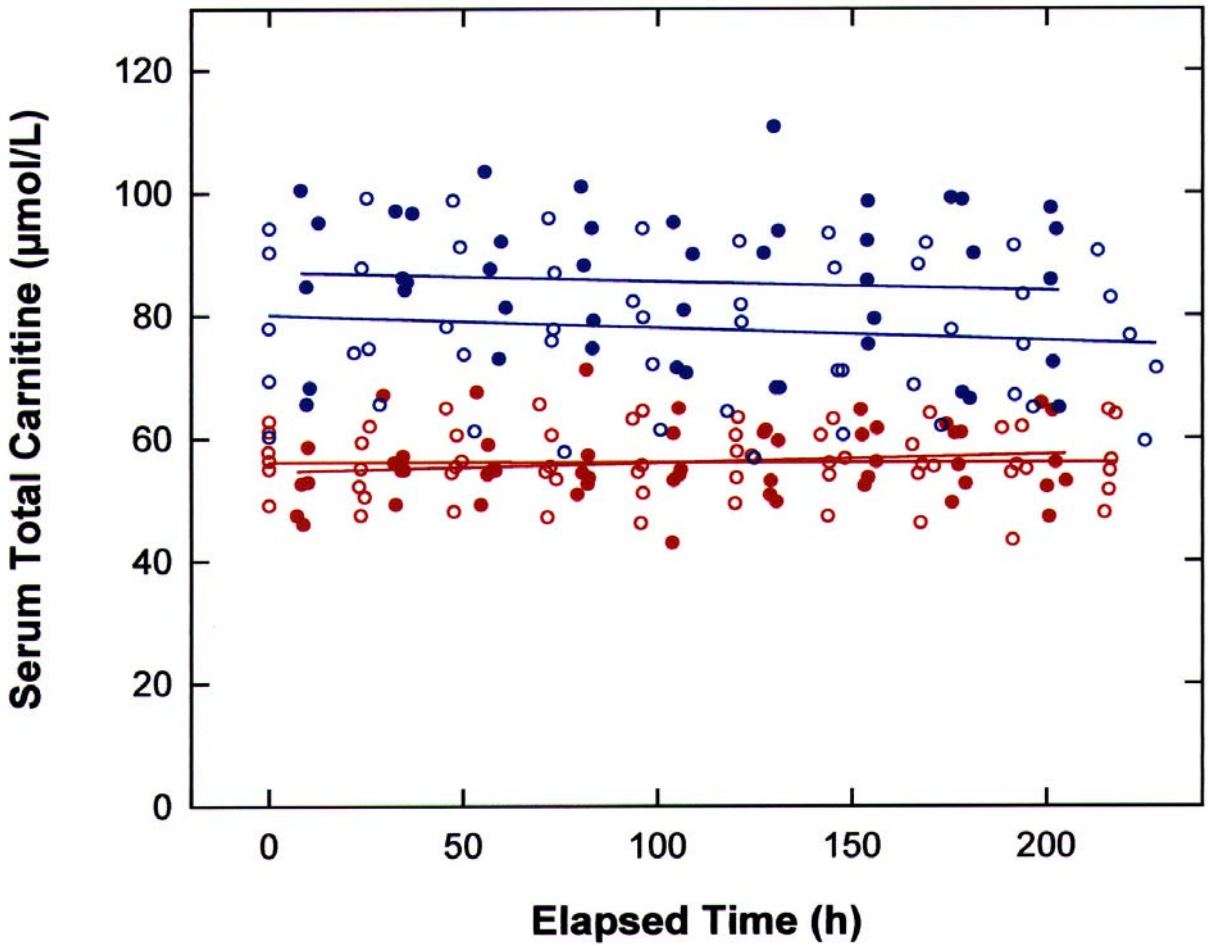
Bioavailability of Oral Carnitine Supplements

Dose	Bioavailability	Reference
2 g	0.16	Harper et al., 1988
6 g*	0.05	Harper et al., 1988
30 and 100 mg/kg	0.16, 0.14	Rizza et al., 1992
100 mg/kg	0.18	Segre et al., 1988
2 g every 12 h	0.14 - 0.16	Sahajwalla et al., 1995
600 mg, 3 times/day	0.17	Rebouche, 1991

Kinetic Parameters for Oral Carnitine Supplements

Dose	T_{max}	$T_{1/2}$	Reference
	(h)	*(h)*	
2 g	4.9	6.5	Harper et al., 1988
30 mg/kg	5.2	1.9	Segre et al., 1988
100 mg/kg	3.7		Segre et al., 1988
30 mg/kg	3.0	3.0	Rizza et al., 1992
100 mg/kg	3.5	4.1	Rizza et al., 1992
2 g	3.1-3.4		Sahajwalla et al., 1995
600 mg	4.0		Rebouche, 1991

Serum Response to Multiple Oral Dosing



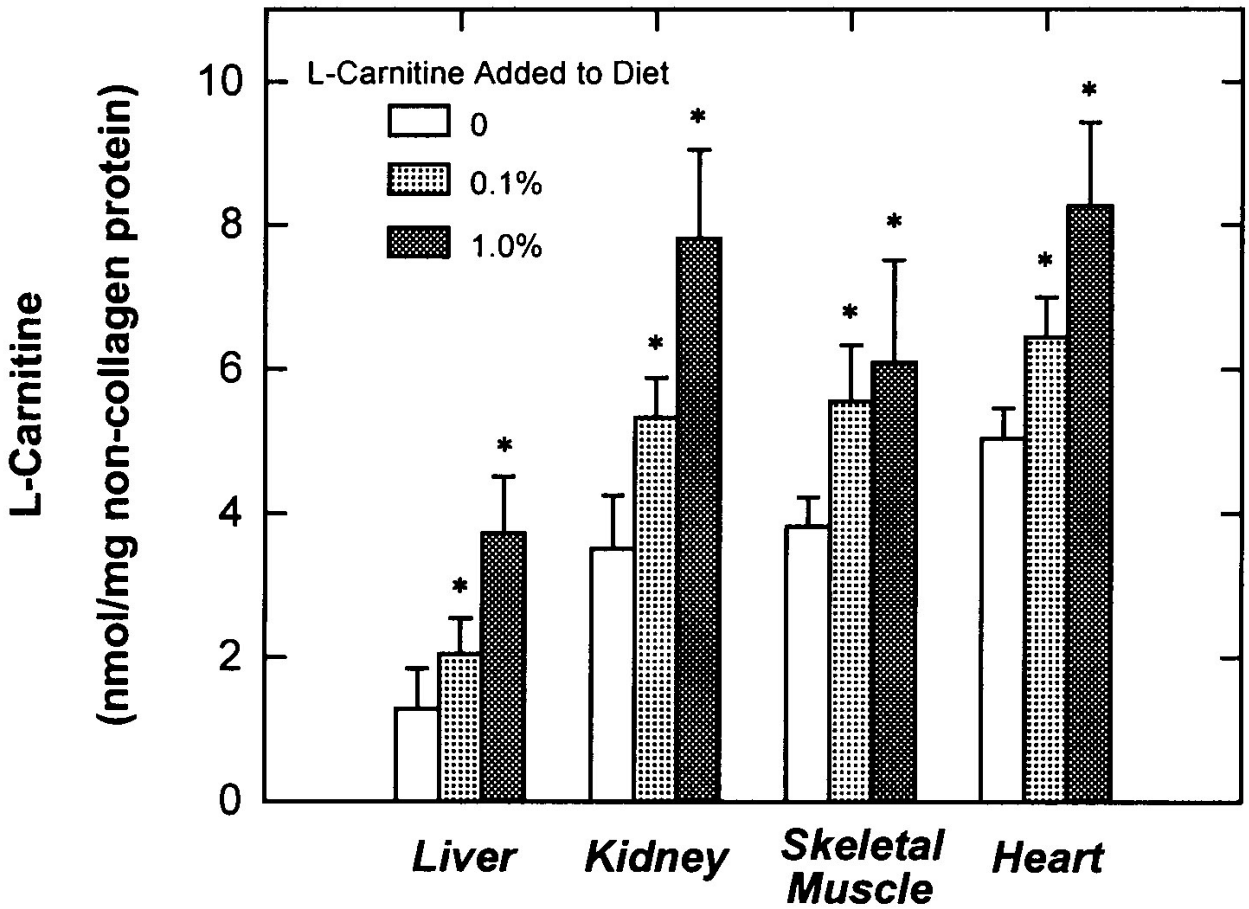
Open circles - 8 am sample

Filled circles - 6 pm sample

Blue circles - carnitine supplement

Red circles - no supplement

Carnitine Supplement in Rats



Data from: Rebouche (1983) J Nutr 113:1906-1913

Carnitine Supplement and Acylcarnitine Ester Appearance

- **Serum acylcarnitine ester concentrations**

  no supplement 7.27 μmol/L

  supplement 13.9 μmol/L

- **Acylcarnitine ester excretion**

  no supplement 3.27 μmol/kg/day

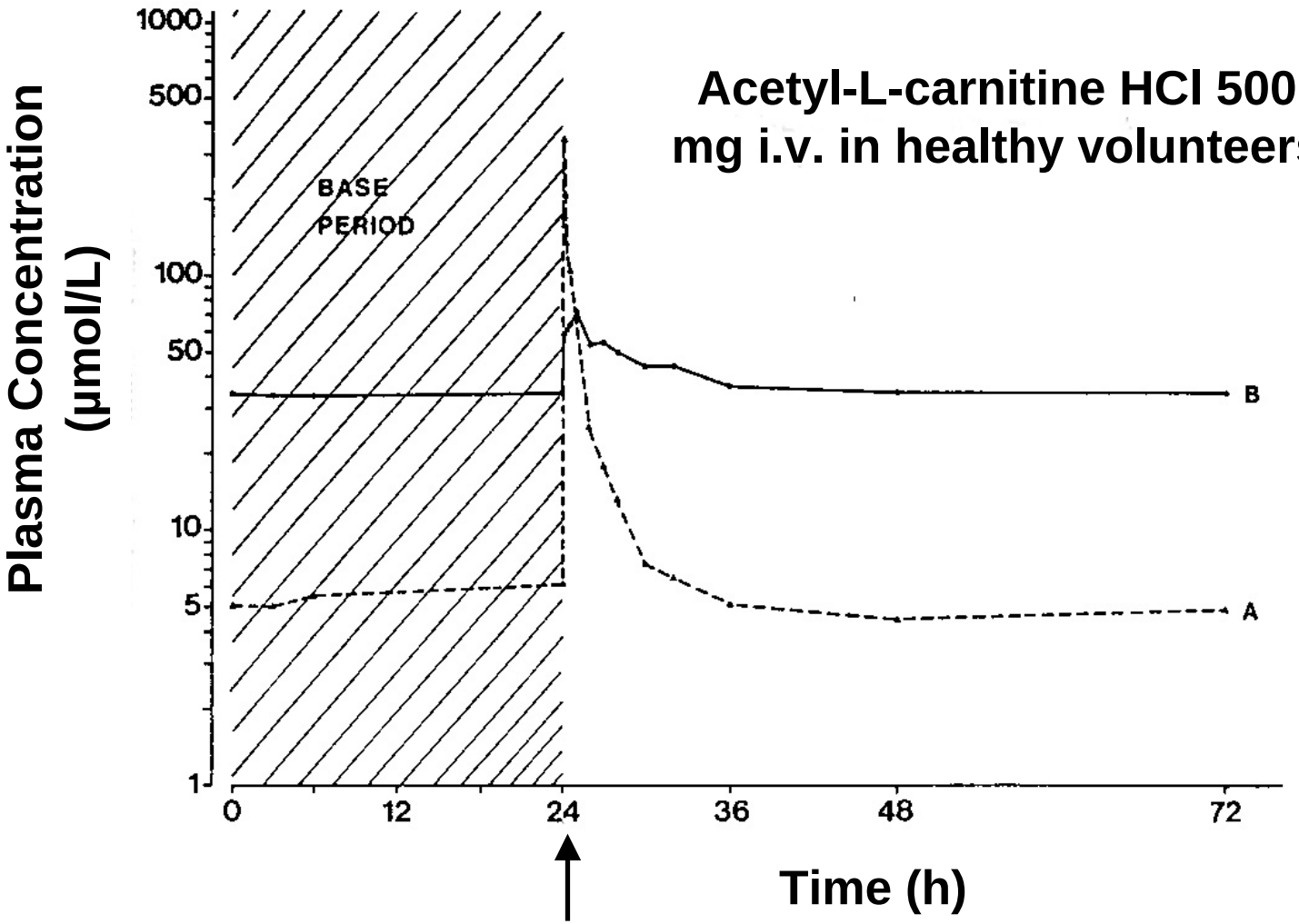
  supplement 6.06 μmol/kg/day

- **Ratio, non-esterified carnitine/total carnitine in urine**

  no supplement 0.58

  supplement 0.62

Acetyl-L-carnitine IV Pharmacokinetics



Acetyl-L-carnitine HCl 500 mg i.v. in healthy volunteers

Data from: Marzo et al. (1989) Eur J Clin Pharmacol 37:59-63

Acetyl-L-carnitine and L-Carnitine Clearance and Interconversions

Renal Clearance

	Sex	Basal	0-12 h	12-24 h
			L/h	
CL_{ALC}	F	0.57	1.40	1.23
	M	0.35	2.08	0.64
CL_{LC}	F	0.14	1.46	0.39
	M	0.24	3.42	0.34

"Clearances of Transformation"

	CL_{ALC-LC}	CL_{LC-ALC}
	L/h	
Females	14.1	2.48
Males	9.04	1.41

Data from: Marzo et al. (1989) Eur J Clin Pharmacol 37:59-63

Future Research Directions

- Do benefits of oral L-carnitine supplements accrue from increase of intracellular carnitine concentrations, or from increased IC/EC carnitine-acylcarnitine exchange?

- Acetyl-L-carnitine supplements: Where do the acetyl and carnitine moieties go, and how much goes intact (as acetyl-L-carnitine)?

Summary and Highlights

- Dietary carnitine is absorbed by active transport and diffusion processes, whereas supplements are absorbed primarily by diffusion. Intracellular acetylation plays a role in the absorption process.
- Renal excretion/reabsorption provides driving force for homeostatic regulation of carnitine metabolism.
- Rapid carnitine-carnitine and carnitine-acylcarnitine ester exchange occurs between tissues and extracellular compartment.
- Repeated dosing L-carnitine supplements are capable of maintaining increased circulating and probably tissue carnitine concentrations.
- Acetyl-L-carnitine supplements are rapidly deacetylated.