The pathways of Insulin Resistance

Exposure and Implications

Ivor Cummins, BE(Chem) CEng MIEI

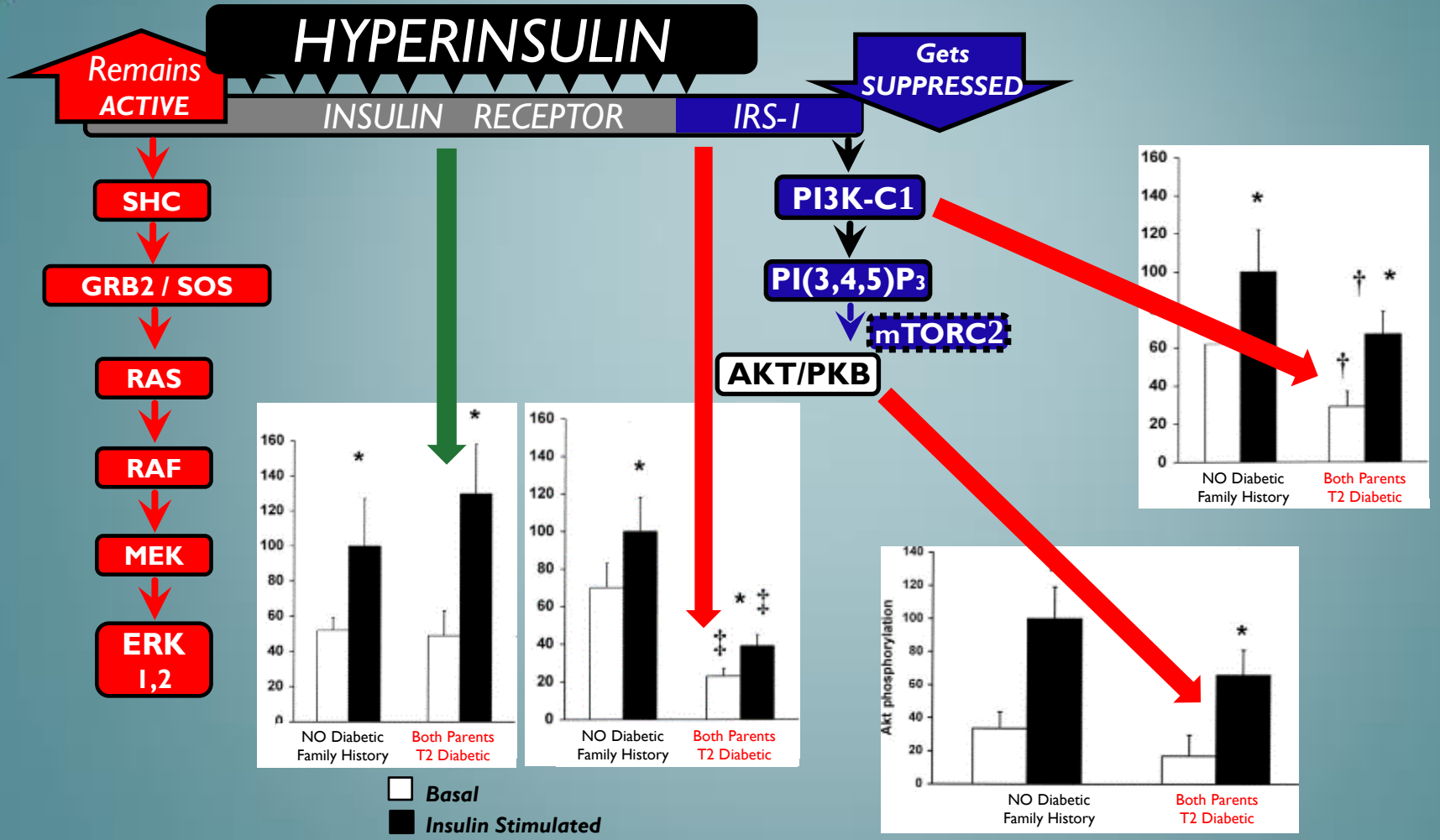
…with special thanks to
***Gabor Erdosi** MSc Molecular Biology / Molecular Genetics*

Disclosure

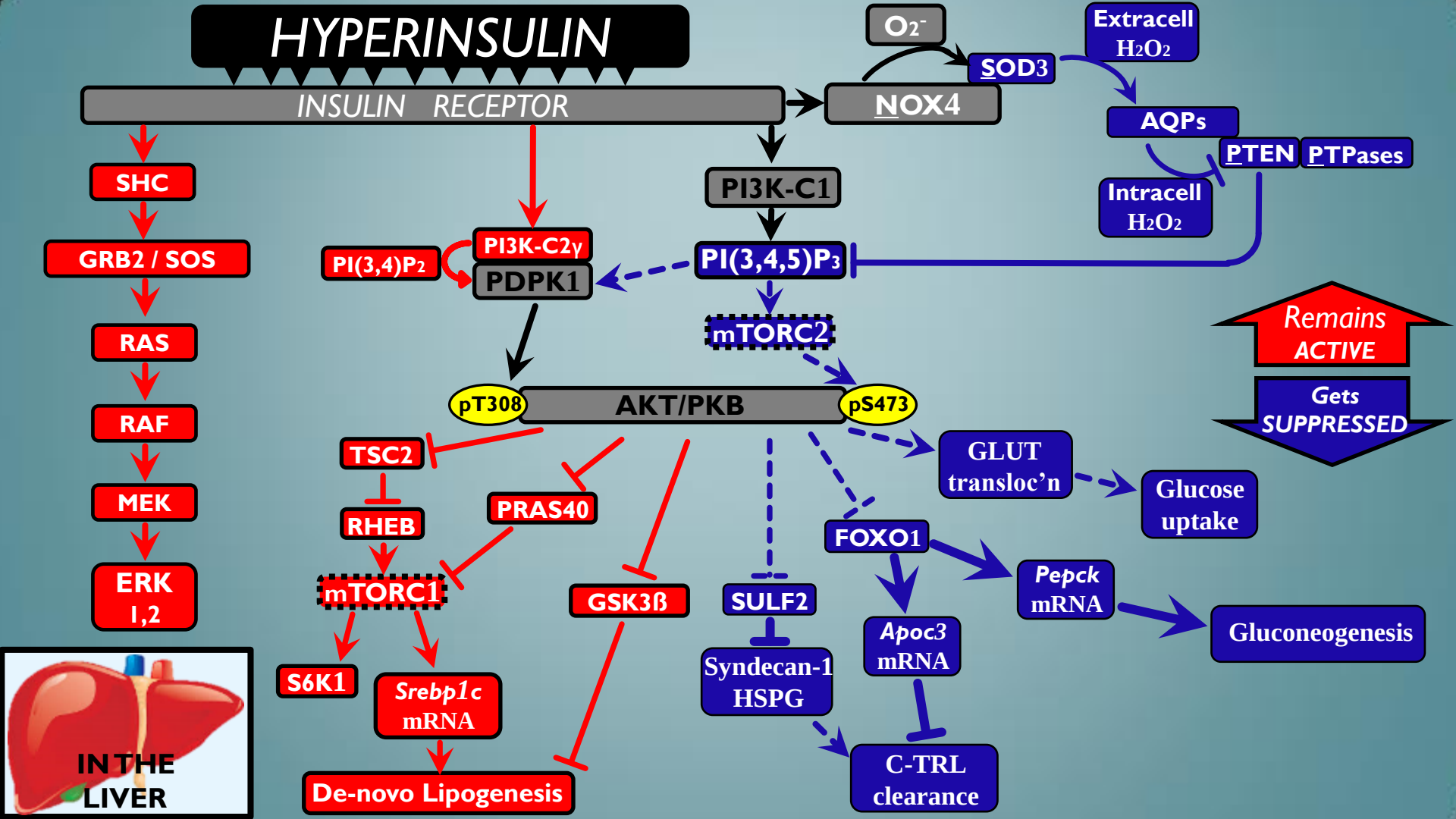
1. My work is supported by David Bobbett and the Irish Heart Disease Awareness (http://www.ihda.ie/)
2. David Bobbett and the IHDA are funding myself and Dr. Gerber's new book which includes the content in this presentation
3. No financial ties to the heart imaging industry (!)

Content

1. The Exposure
2. Paths to Hyperinsulinemia / IR
3. The Power of the CAC Score
   & a word on LDL, the ‘bad cholesterol”
4. Wrapup



Skeletal Muscle Insulin Resistance in Normoglycemic Subjects With a Strong Family History of Type 2 Diabetes Is Associated With Decreased Insulin-Stimulated Insulin Receptor Substrate-1Tyrosine Phosphorylation *DIABETES, VOL. 50, NOVEMBER 2001*


HYPERINSULIN
INSULIN RECEPTOR
SHC
GRB2 / SOS
RAS
RAF
MEK
ERK 1,2
PI3K-C1
PI3K-C2γ
PI(3,4)P2
PDPK1
PI(3,4,5)P3
mTORC2
pT308
AKT/PKB
pS473
TSC2
RHEB
mTORC1
PRAS40
S6K1
Srebp1c mRNA
De-novo Lipogenesis
GSK3ß
SULF2
Syndecan-1 HSPG
C-TRL clearance
FOXO1
Apoc3 mRNA
Pepck mRNA
Gluconeogenesis
GLUT transloc'n
Glucose uptake
O2-
SOD3
NOX4
Extracell H2O2
AQPs
PTEN
PTPases
Intracell H2O2
Remains ACTIVE
Gets SUPPRESSED
IN THE LIVER

H

IN

SHC

GRB2 / SOS

RAS

RAF

MEK

ERK 1,2

S6

IN THE LIVER

racell $_2O_2$

AQPs

PTEN

PTPases

racell H_2O_2

Remains ACTIVE

Gets SUPPRESSED

Glucose uptake

Gluconeogenesis

PART I

THE EXPOSURE

Dr. Joseph R. Kraft, MD, MS, FCAP

1922 – 2017

Chairman, Department of Clinical Pathology and Nuclear Medicine,
St. Joseph's Hospital 1962-1990 (appointed Chairman Emeritus on retirement)

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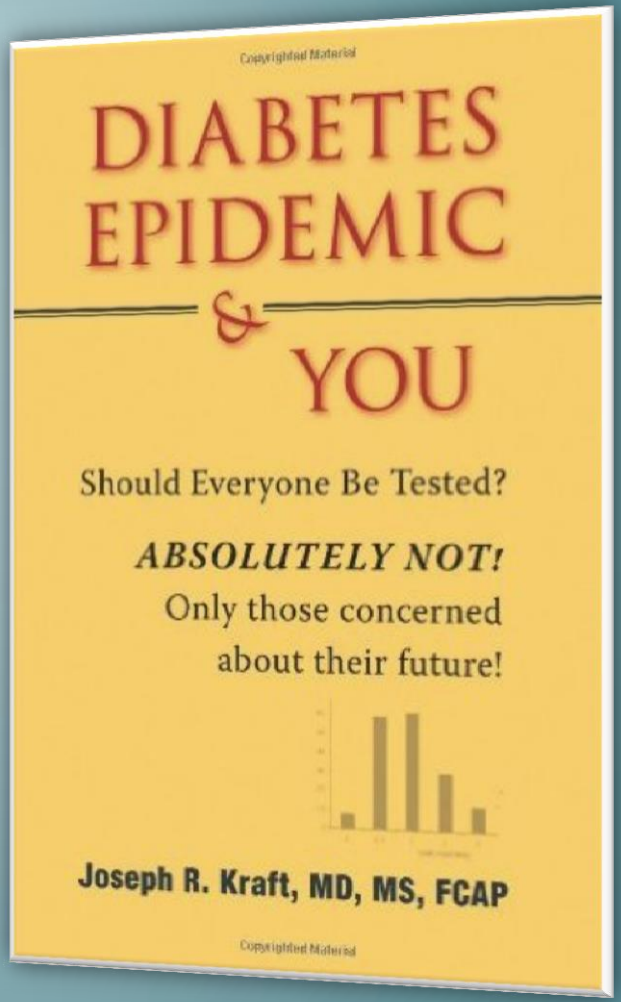

Hyperinsulinemia and Insulin Resistance:

"They are not combatants.

***They are one and the same*.”**

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The Kraft “Diabetes In Situ” Test

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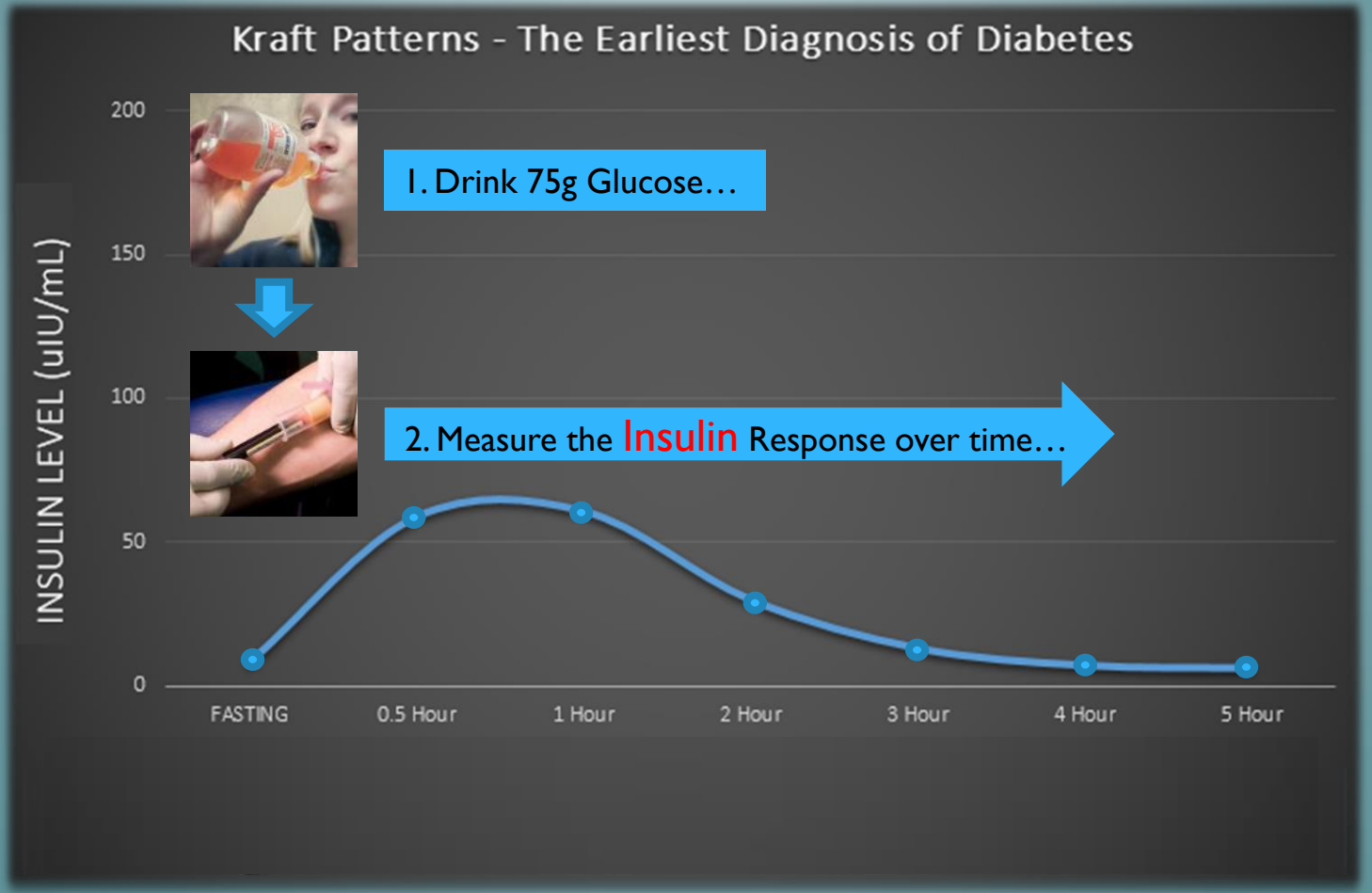
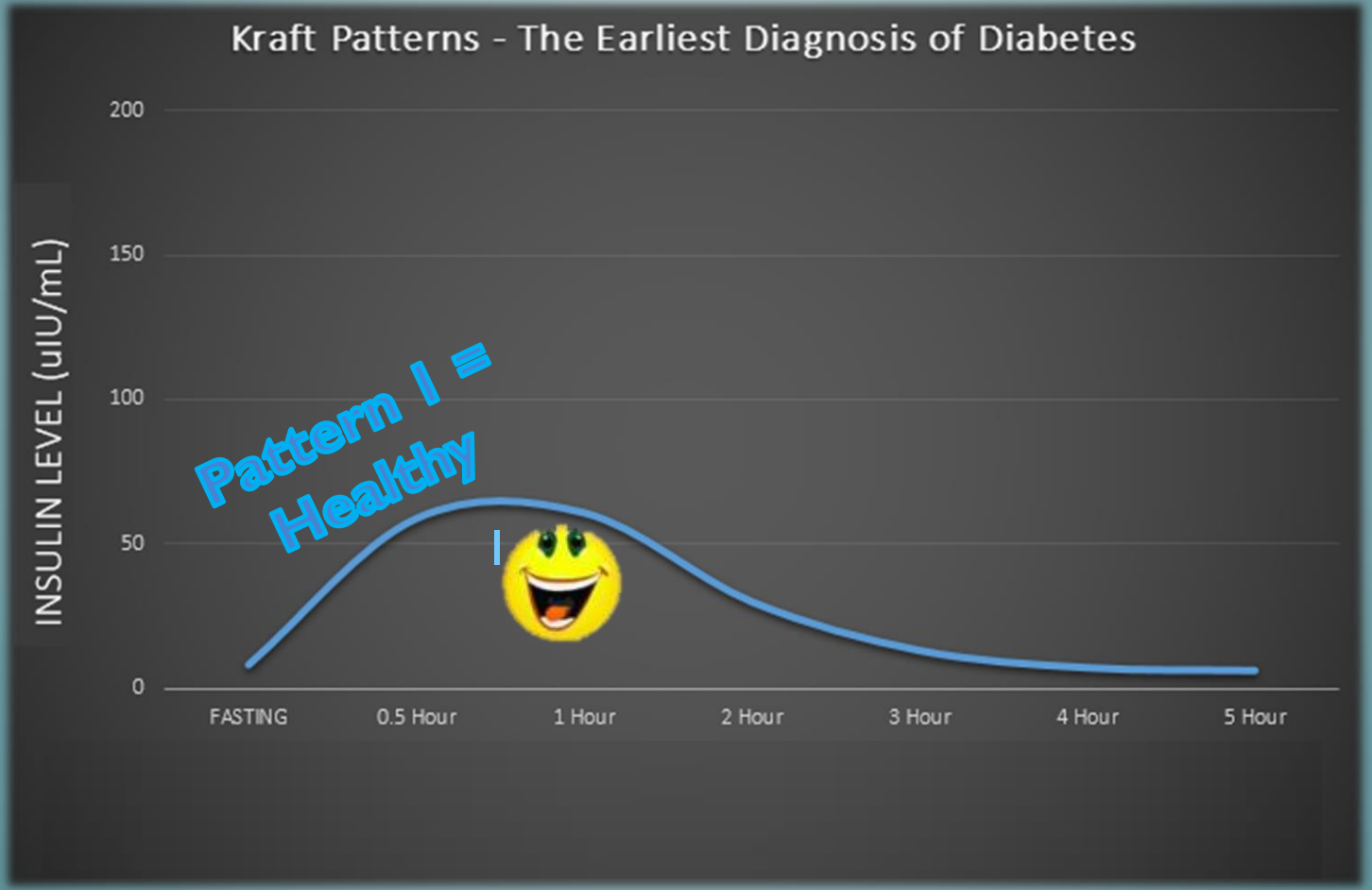
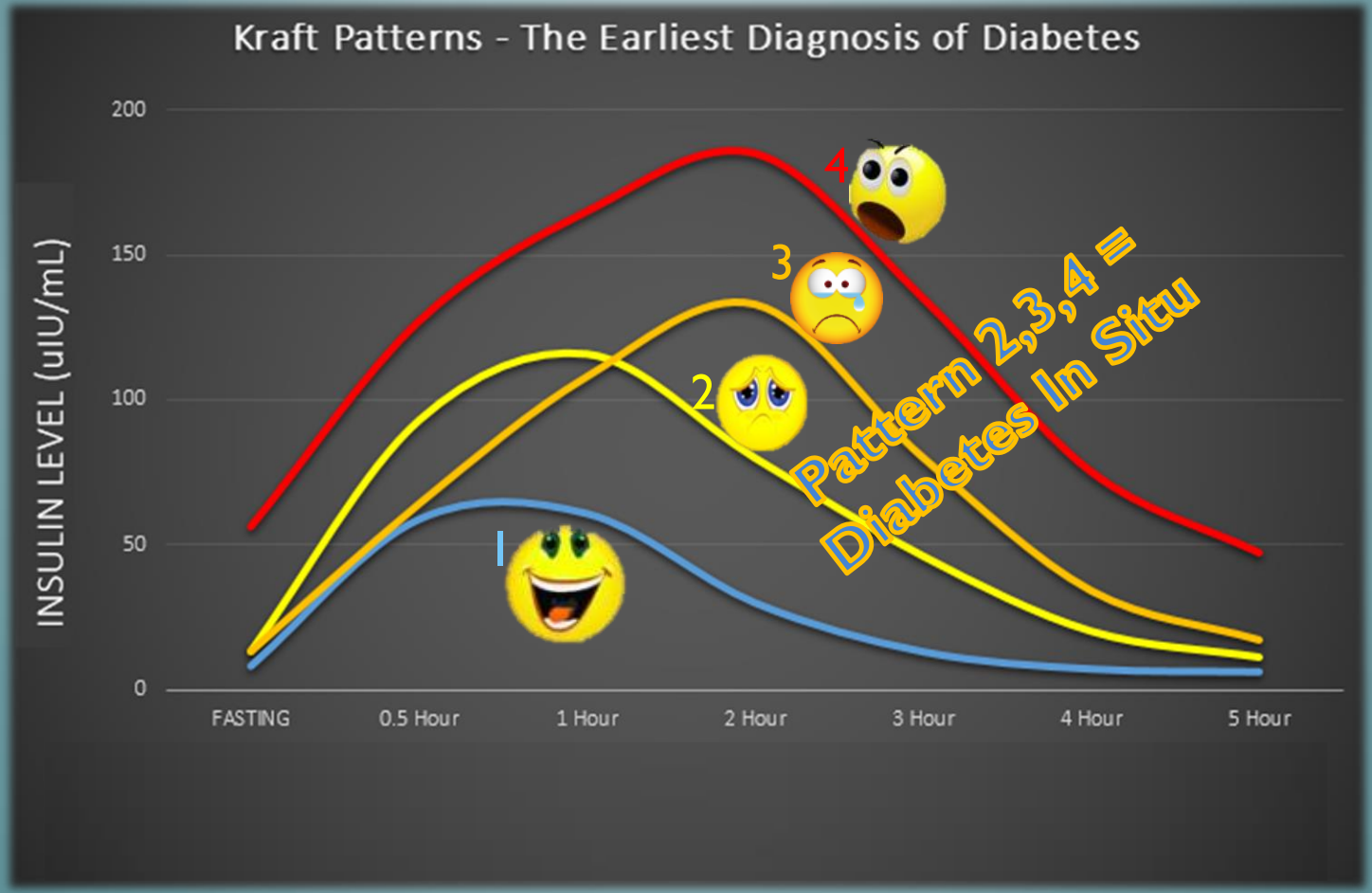


Kraft Pattern I- Euinsulinemia (Non-Diabetic)



Kraft Pattern 2, 3, 4 - Hyperinsulinemia (Diabetes in Situ)



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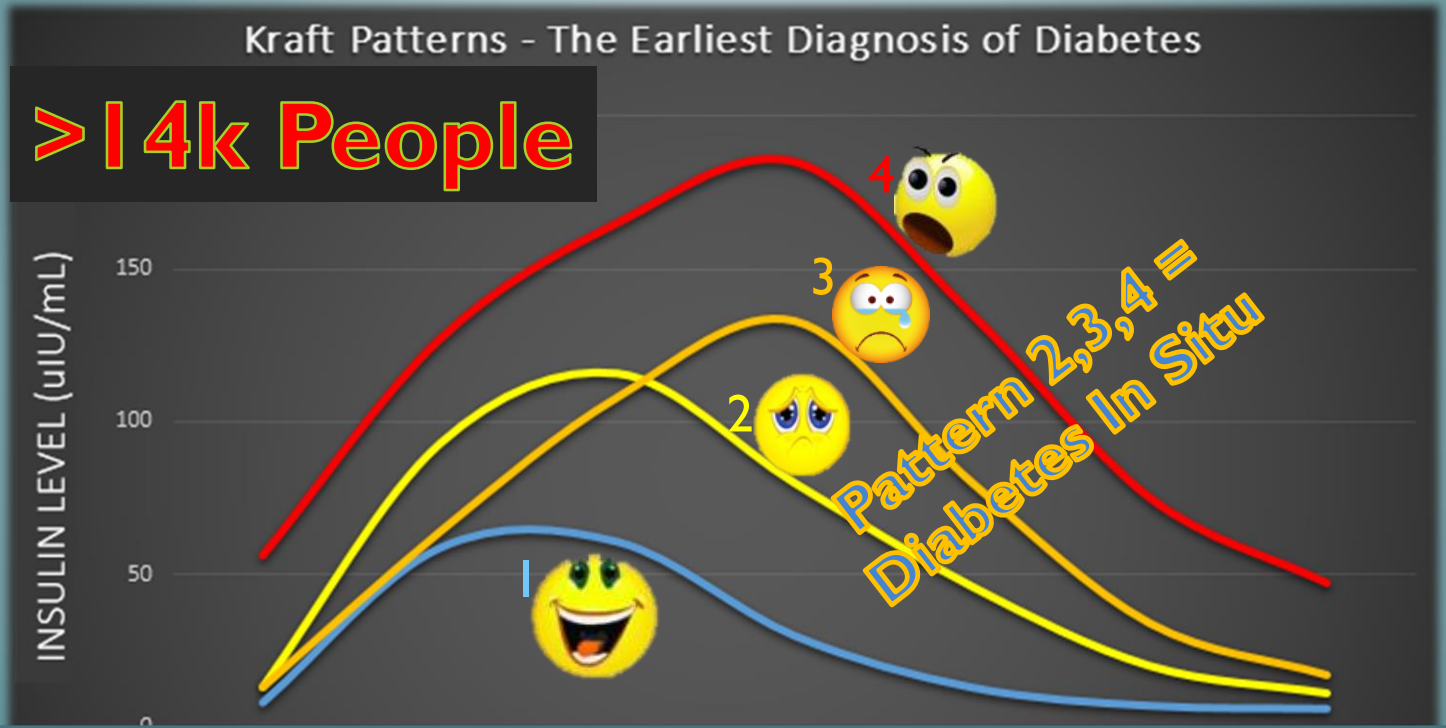
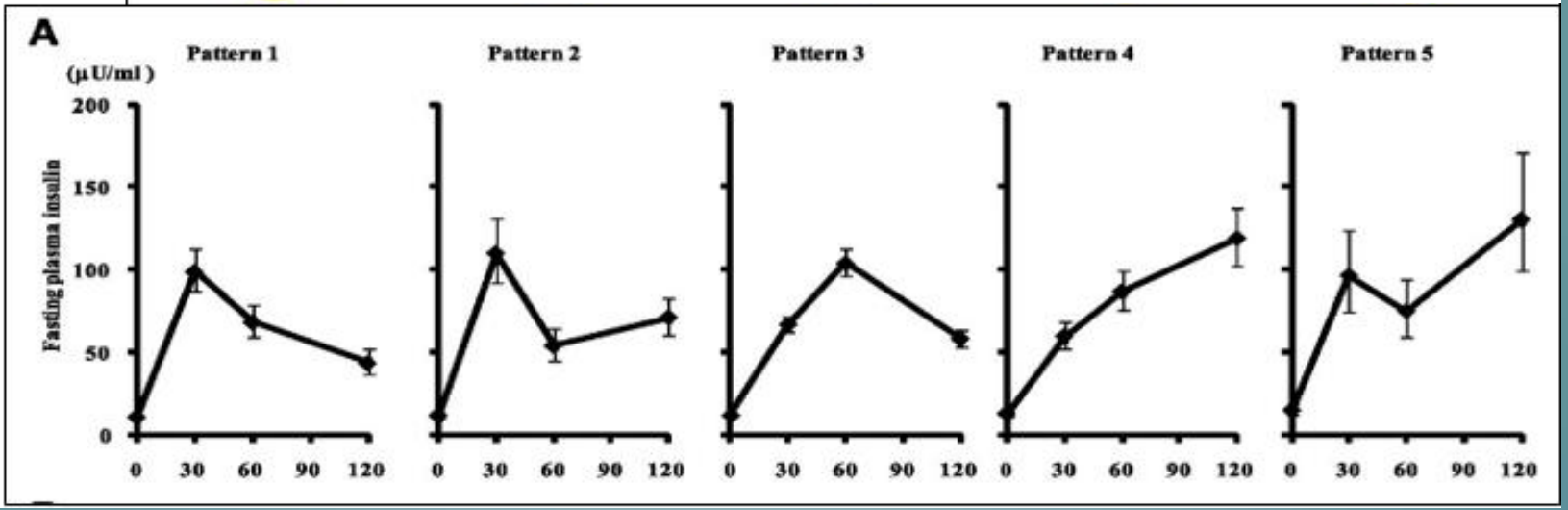


"The Earliest Laboratory Diagnosis for Diabetes" - Dr. Joseph R. Kraft

Kraft predicts Full-blown T2D…2013 Study

	Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5
DIABETES INCIDENCE ***11 Years Later***	3%				

ORIGINAL



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DIABETES CARE, VOLUME 36, MAY 2013

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3%	10%	15%		



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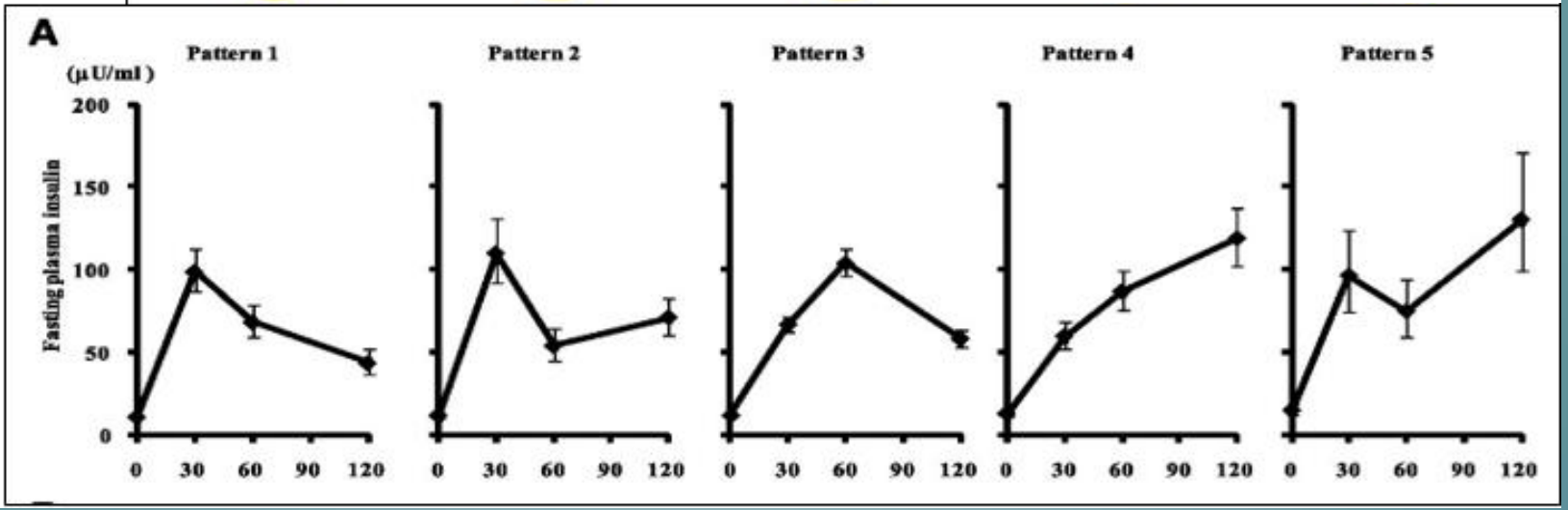

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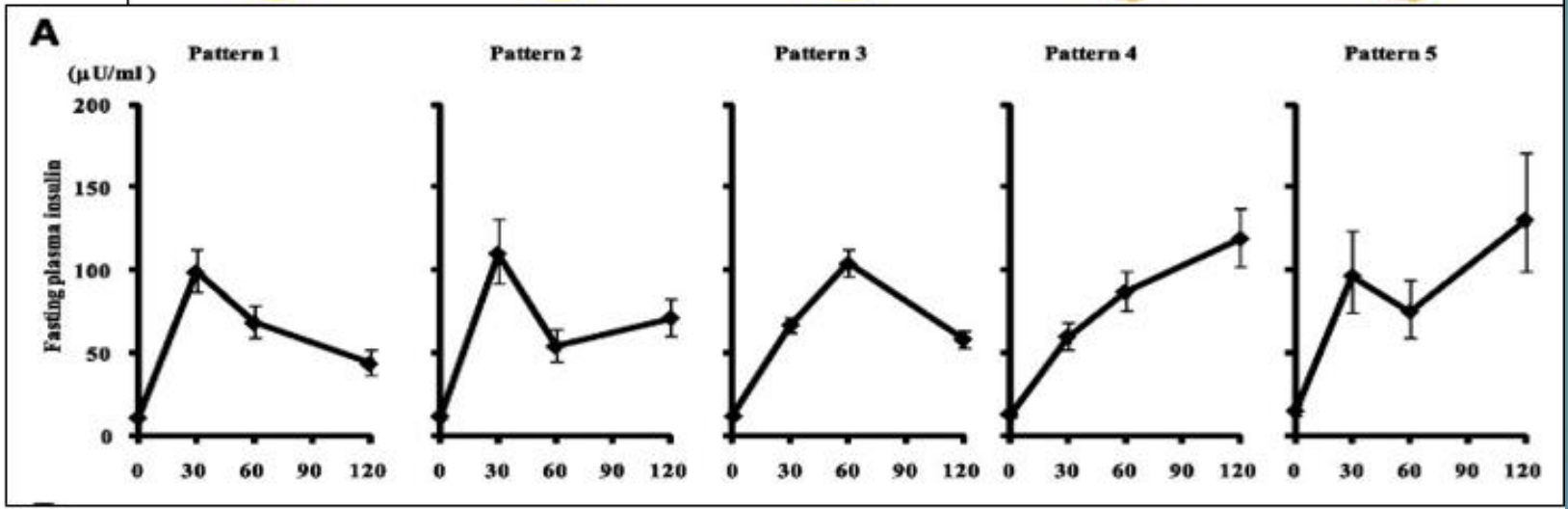
Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5
3%	10%	15%	48%	38%



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And did you know…

That 49%-52% in the US are now…

pre-Diabetic or Diabetic.

Pre-Diabetic ≈ Diabetic ≈ Insulin Resistant ≈ Hyperinsulinemic

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Using Kraft's test, probably >65% would have

Hyperinsulinemia / Diabetes In Situ

Menke A, et al. JAMA. 2015;31[illegible]).1021-1029. doi:10.1001/jama.2015.10029.

And did you know…

"Those with cardiovascular disease not identified with diabetes… are simply undiagnosed" - Dr. Joseph R. Kraft

Using Kraft's test, many more would have Hyperinsulinemia / Diabetes In Situ

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Latest Data…2015 Study

Diabetes and Heart Disease – Terrible Twins

Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV--a survey from the European Society of Cardiology

European Heart Journal, 02/12/2015 **Evidence Based Medicine Clinical Article**

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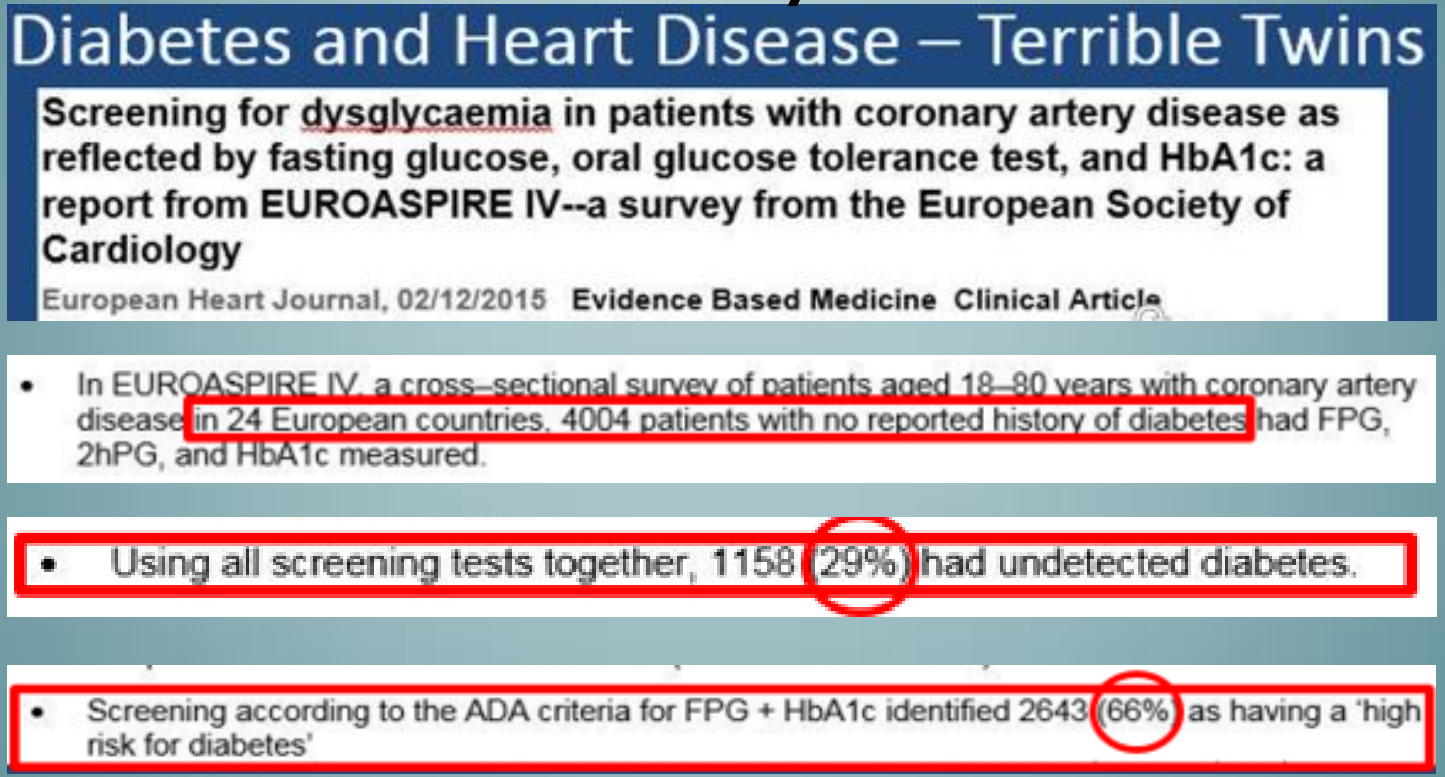
- Using all screening tests together, 1158 (29%) had undetected diabetes.

- Screening according to the ADA criteria for FPG + HbA1c identified 2643 (66%) as having a 'high risk for diabetes'

Latest Data…2015 Study



I'd be surprised if many of the remaining 34% would pass a Kraft Test…!

Very Latest Data…Feb 15th 2017 - Medscape

Cardiology

CVD Burden in U.S. Expanding Faster Than Expected

— 2015 saw levels once projected for 2030, report says

The growth in cardiovascular disease has outpaced expectations, reaching a prevalence of 41.5% in 2015 -- 15 years ahead of schedule, according to a report from the American Heart Association (AHA).

"So in short, the burden of CVD is growing faster than our ability to combat it," he said -- and the projections suggested it will get worse.

What about Hyperinsulinemia/IR versus Cholesterol …as cause of CVD?

What do Leading-Edge Experts Say?

- 'Cholesterol and Disease' Experts are called ***'Lipidologists'***
- One of the USA's foremost is Thomas Dayspring, MD, FACP, FNLA, NCMP
  - Clinical Assistant Professor of Medicine, Director of Cardiovascular Education

In reply to Ivor Cummins

Thomas Dayspring @Drlipid · 11 Nov 2014

@FatEmperor Current NHANES data: majority of MI are explained by IR. But real message is unless >200 mg/dL - LDLc is terrible biomarker

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1) ***In reality, the majority of Heart Attacks are due to*** **INSULIN RESISTANCE**

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My translation:

1) ***In reality, the majority of Heart Attacks are due to INSULIN RESISTANCE***

2) ***LDL is a near-worthless predictor for cardiovascular issues****

*(people with LDLc above 200mg/dL, or 5.3mmol/L are rare…)

So what is this 'Insulin Resistance' thing then?

Well, if this is 'LDL' as a causal driver of Coronary Vascular Disease…

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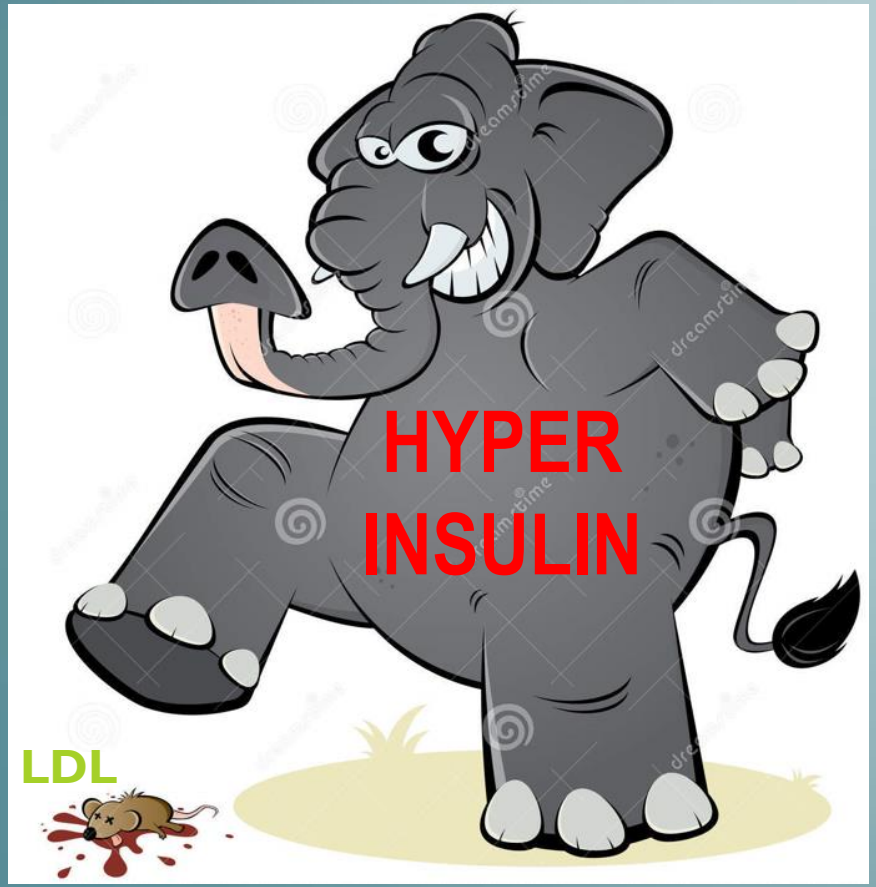


...then this is INSULIN RESISTANCE !

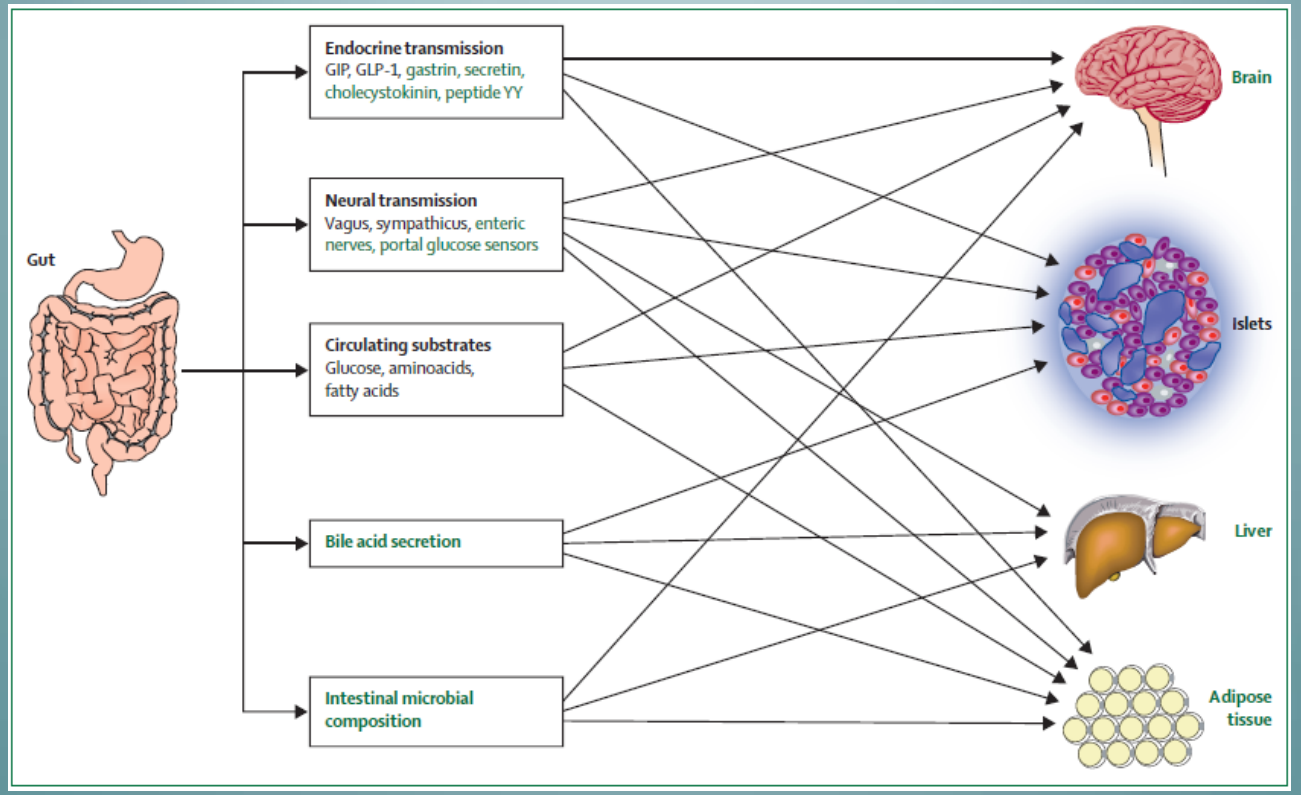
Well, if this is 'LDL' as a causal driver of Coronary Vascular Disease...

PART 2

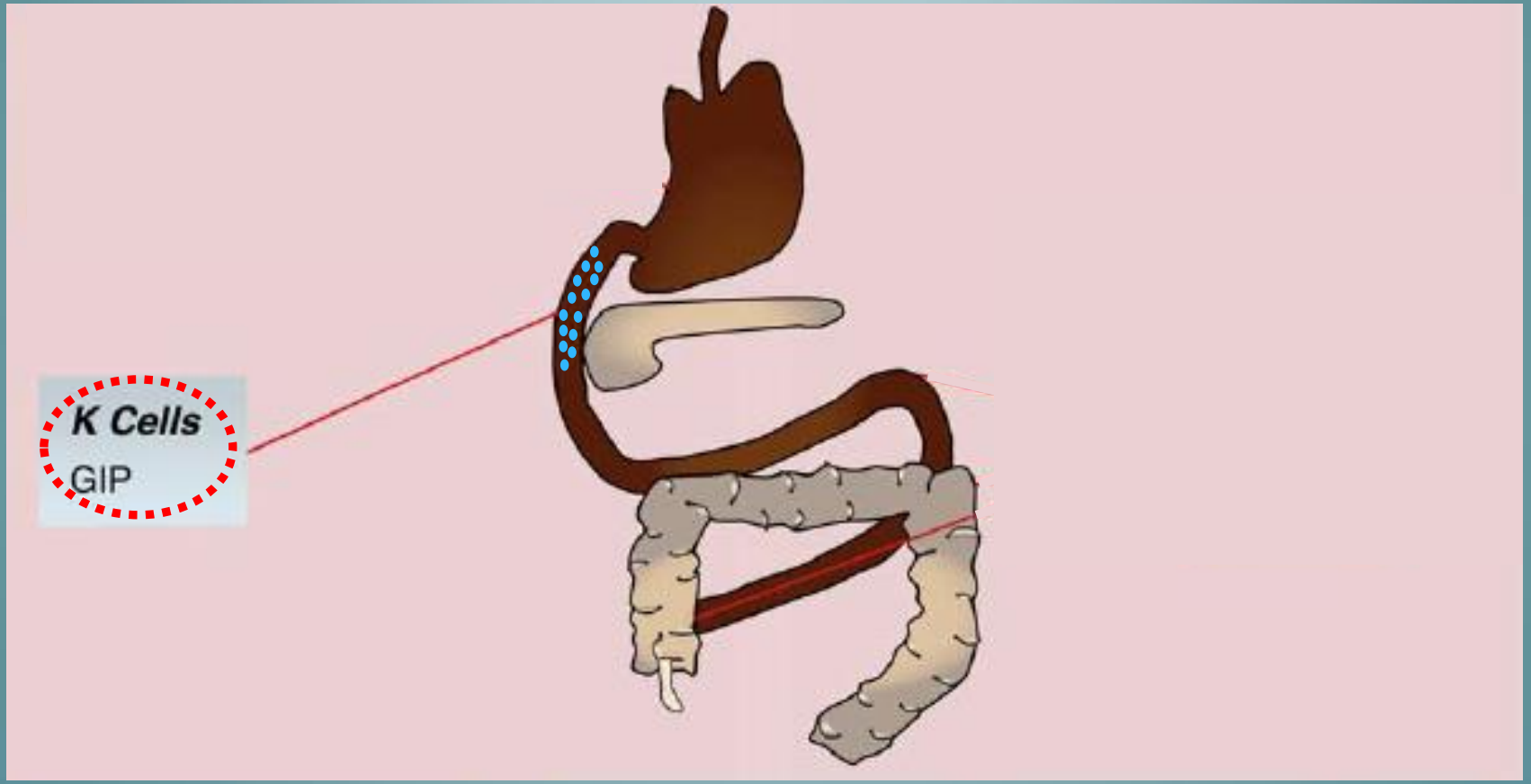
Paths to Hyperinsulinemia / IR

Pathway to Hyperinsulinemia/IR

"The Gut is Ground Zero"



Intestinal Imperatives – and the Incretin Effect



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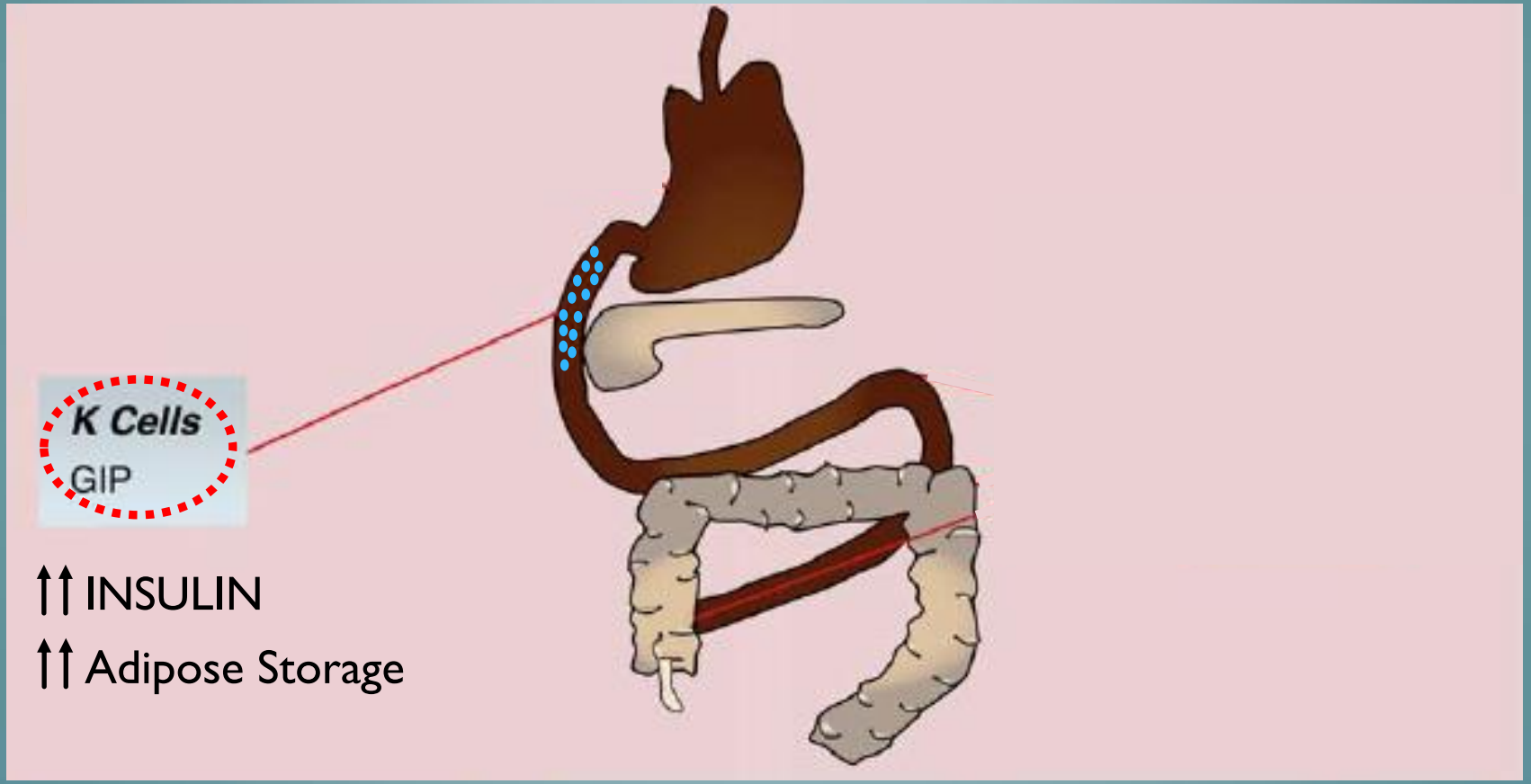

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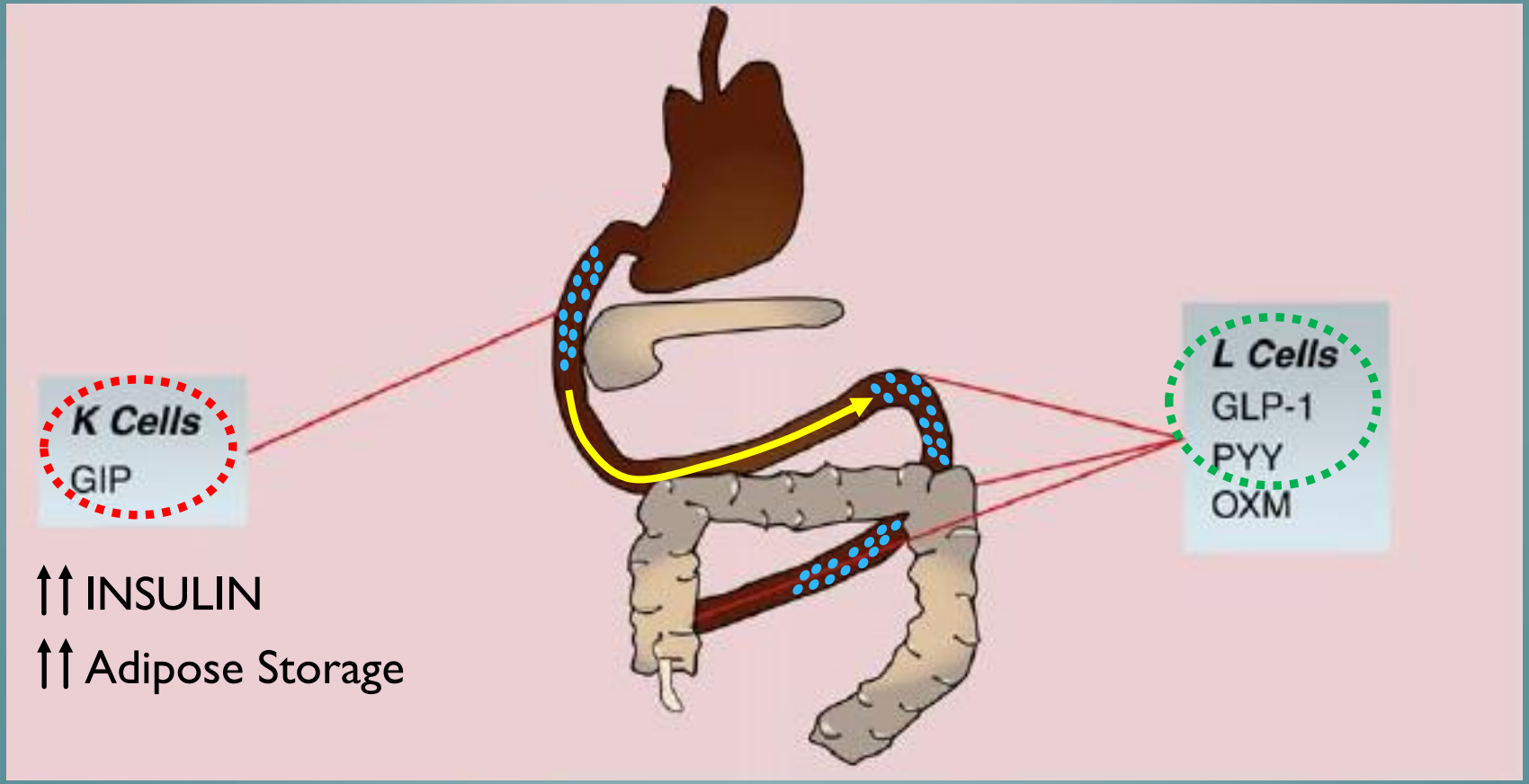

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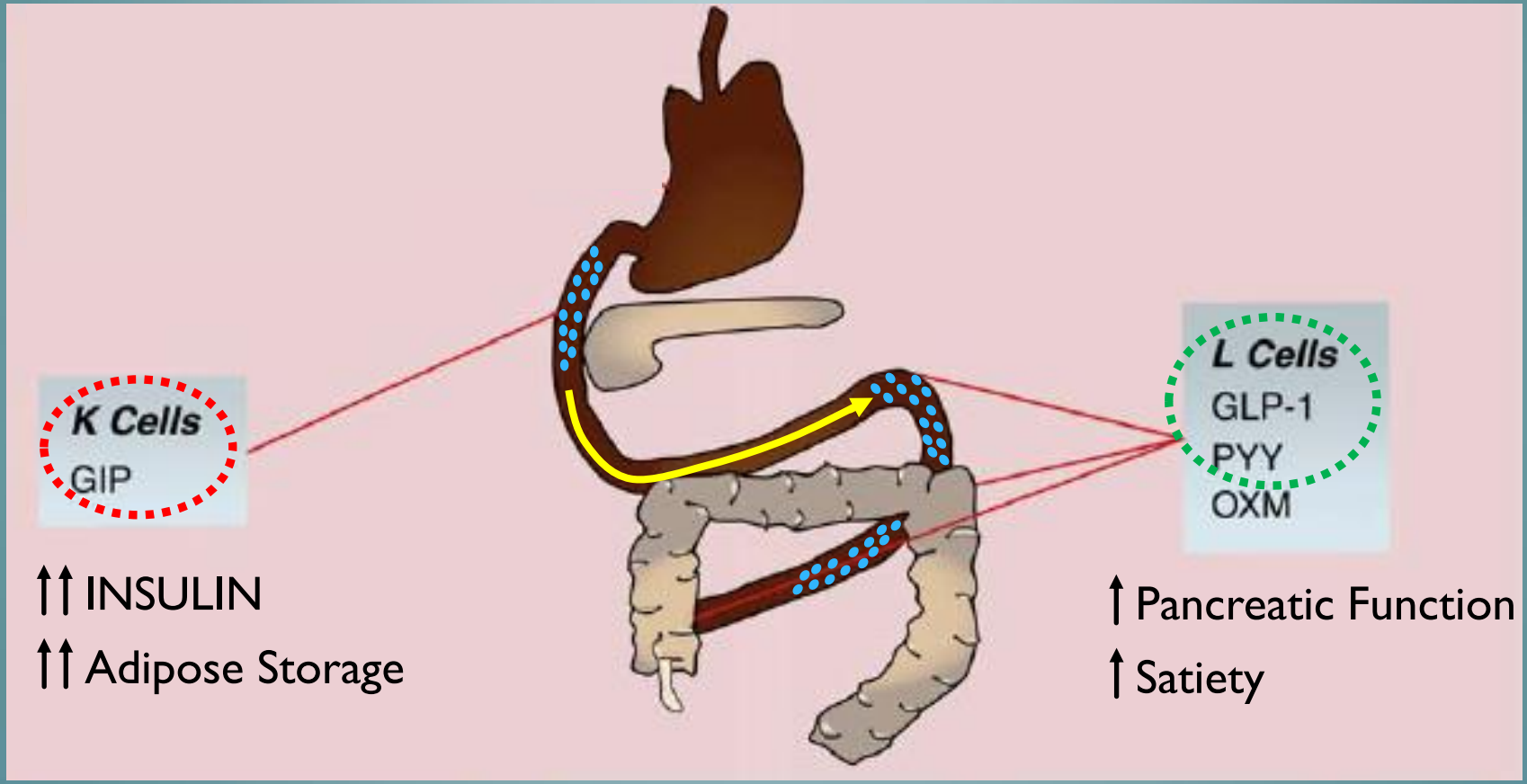

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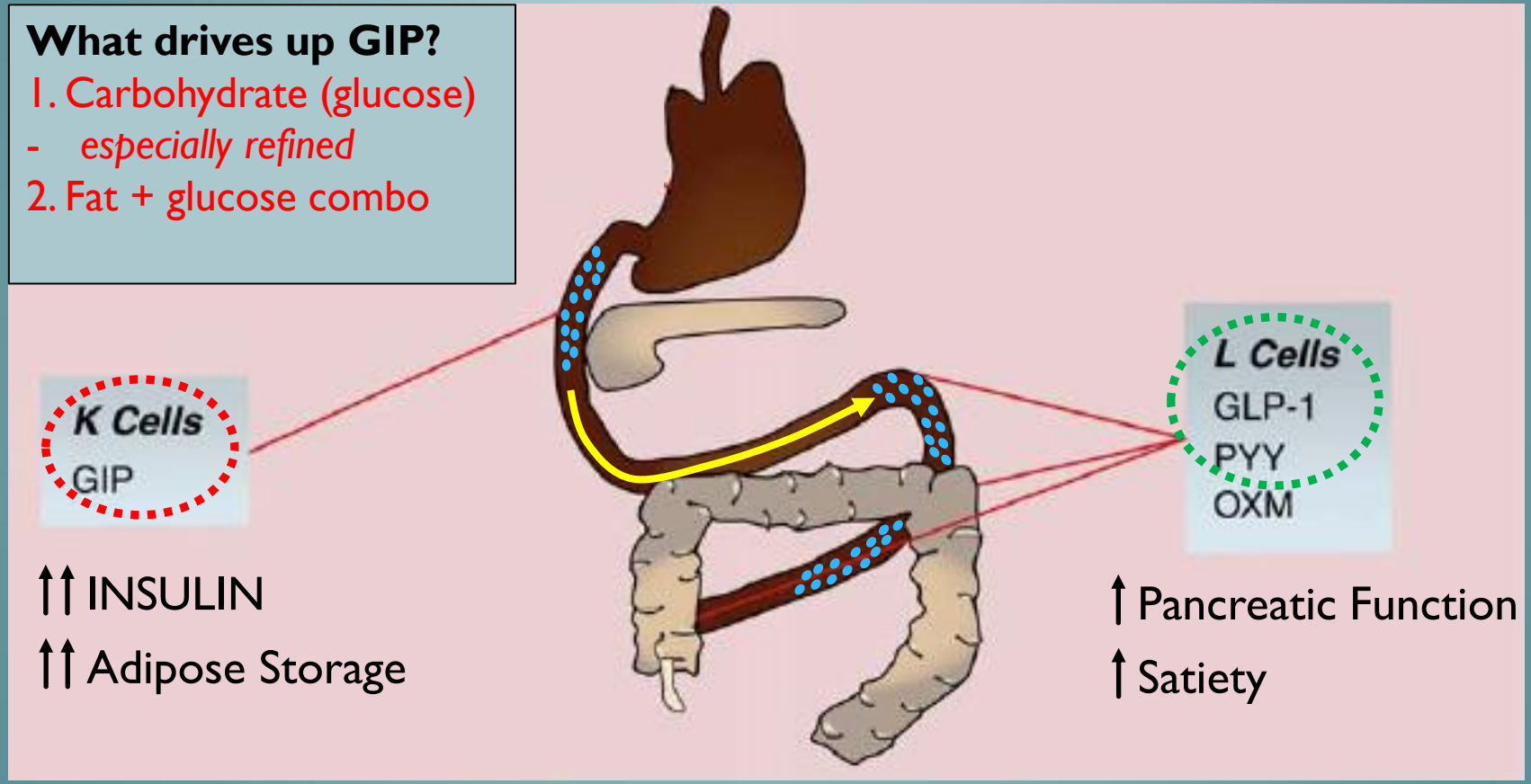
What drives up GIP?

1. Carbohydrate (glucose)
   - *especially refined*
2. Fat + glucose combo



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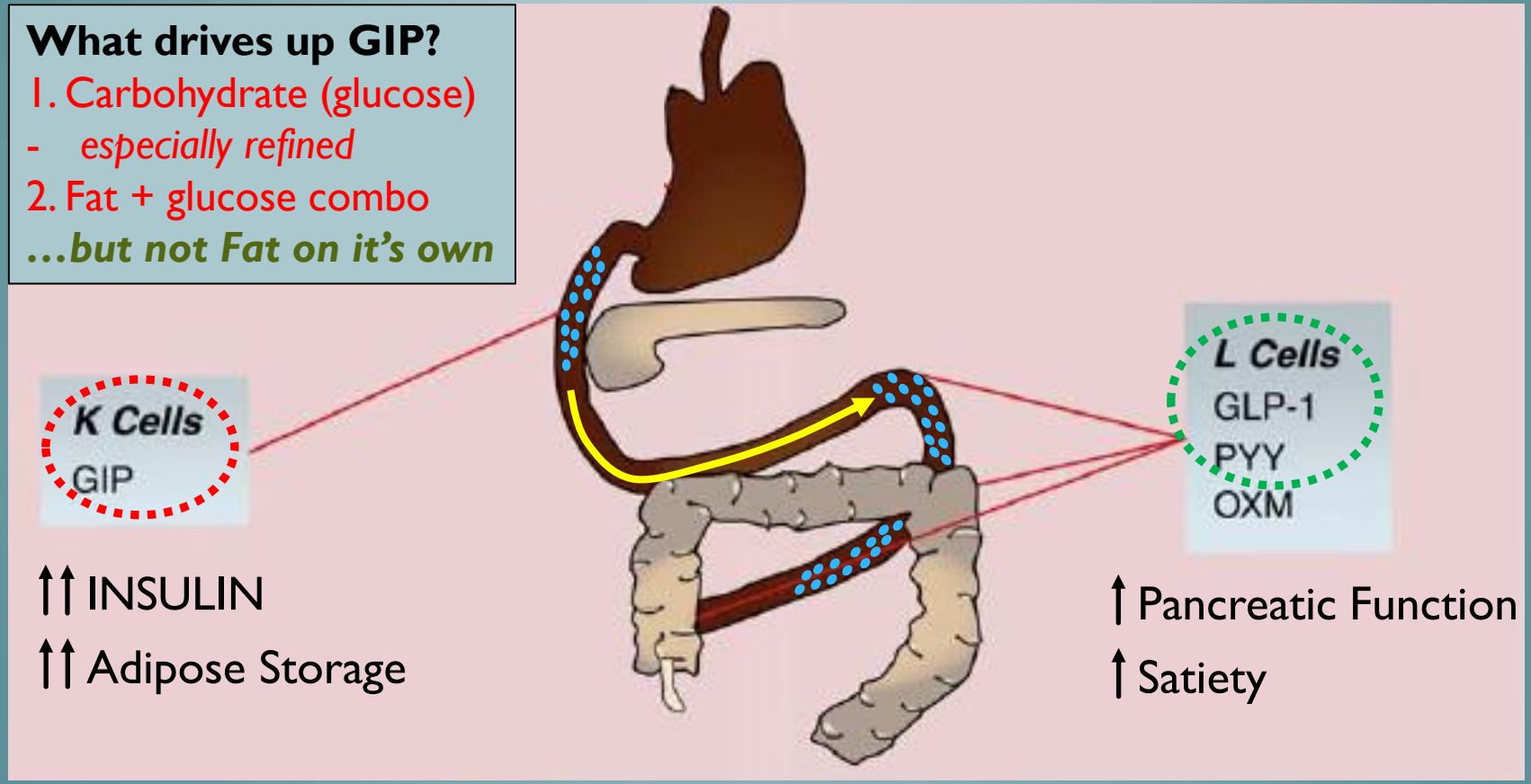
…but not Fat on it's own



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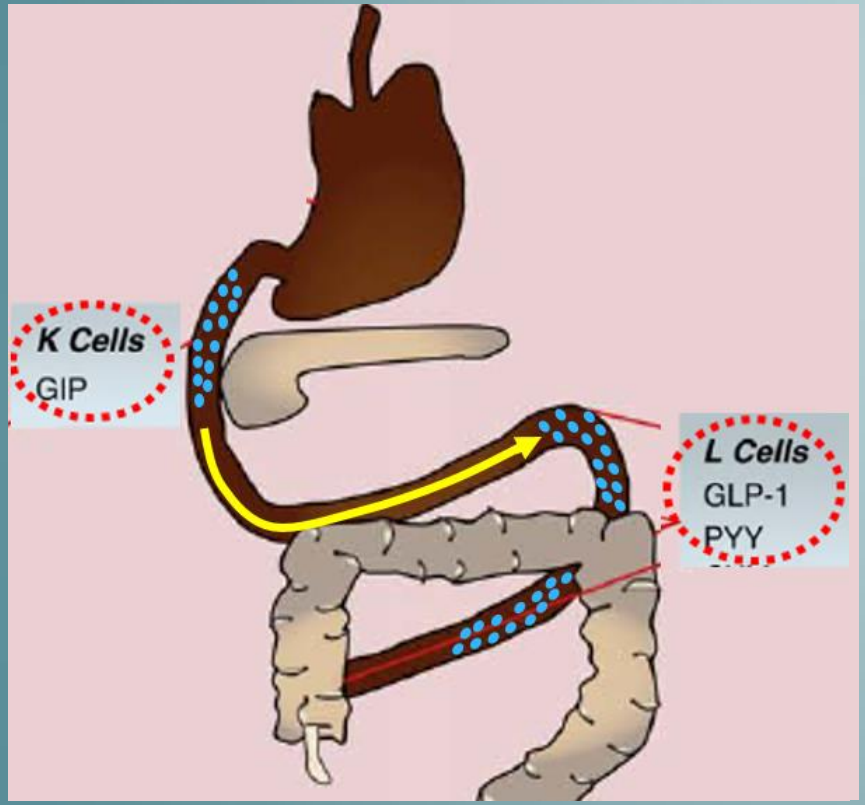
What can Gastric Bypass Surgery outcomes tell us?



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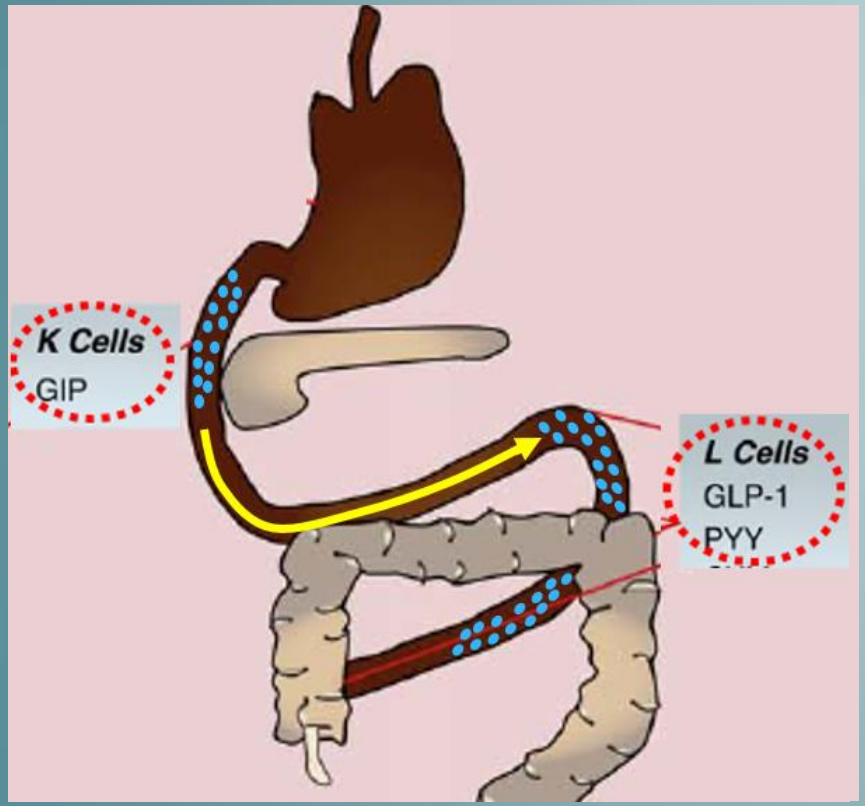

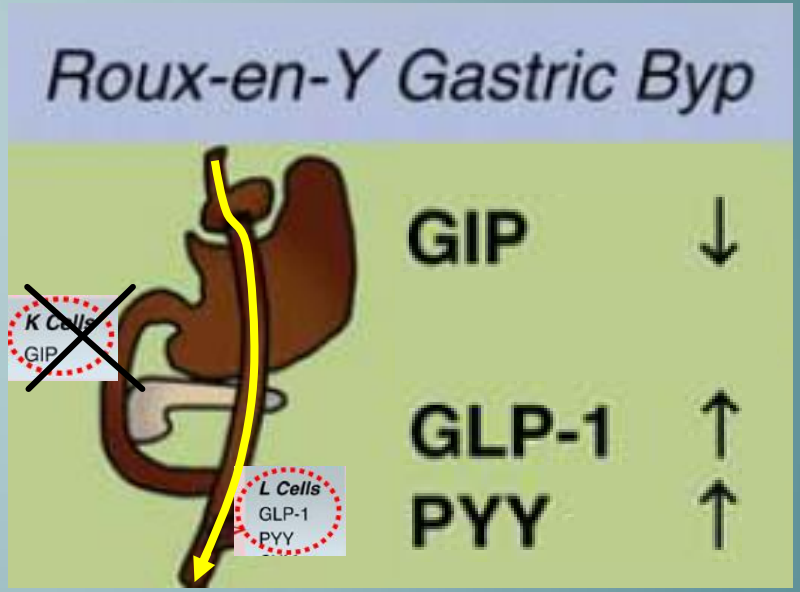

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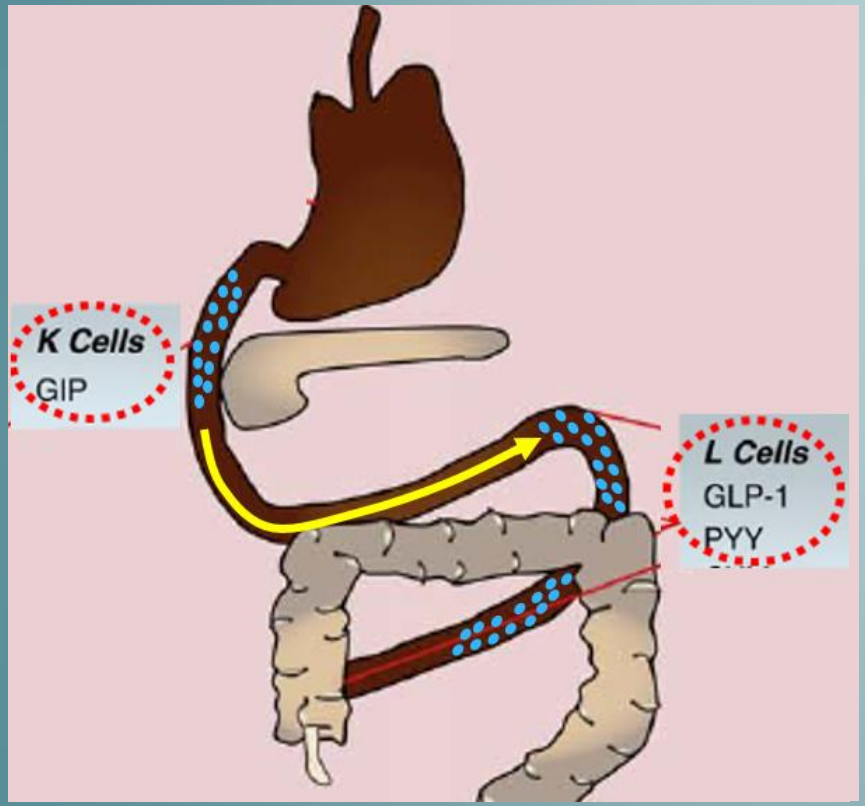

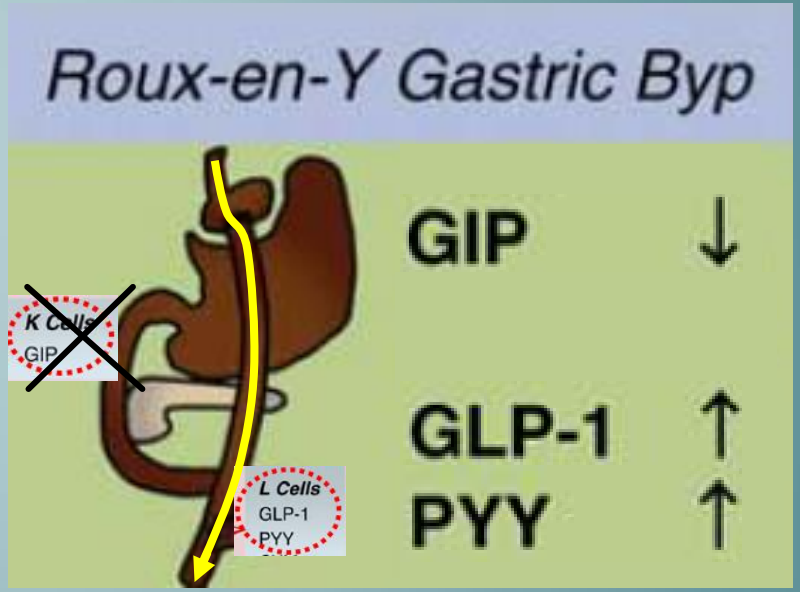

- GIP, GLP-1 & PYY resolve Blood Glucose control – **way ahead of weight loss**
- The "Diabetic" GIP to GLP-1 & PYY ratio is reversed – **signaling is restored**

Effect of Modified Roux-en-Y Gastric Bypass Surgery on GLP-1, GIP in Patients with Type 2 Diabetes Mellitus
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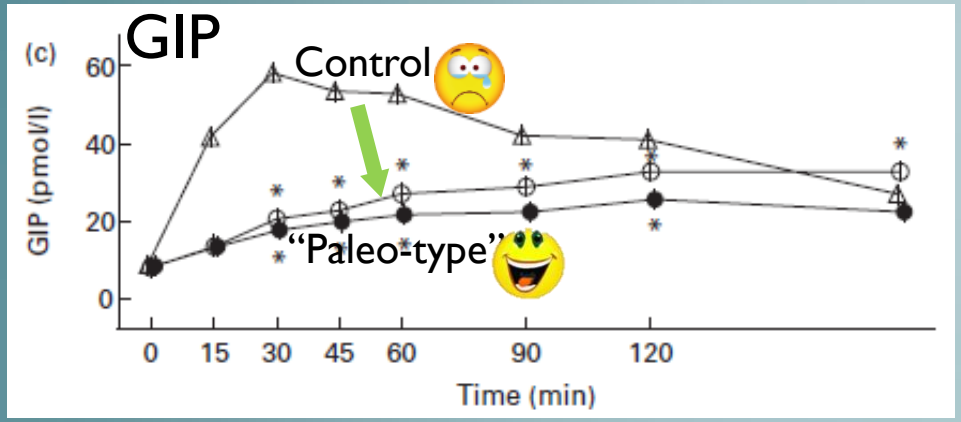
So surgery does the trick - but what can **Diet** do?



Plant-rich mixed meals based on Palaeolithic diet principles have a dramatic impact on incretin, peptide YY and satiety response, but show little effect on glucose and insulin homeostasis: an acute-effects randomised study *British Journal of Nutrition (2015), 113, 574–584*

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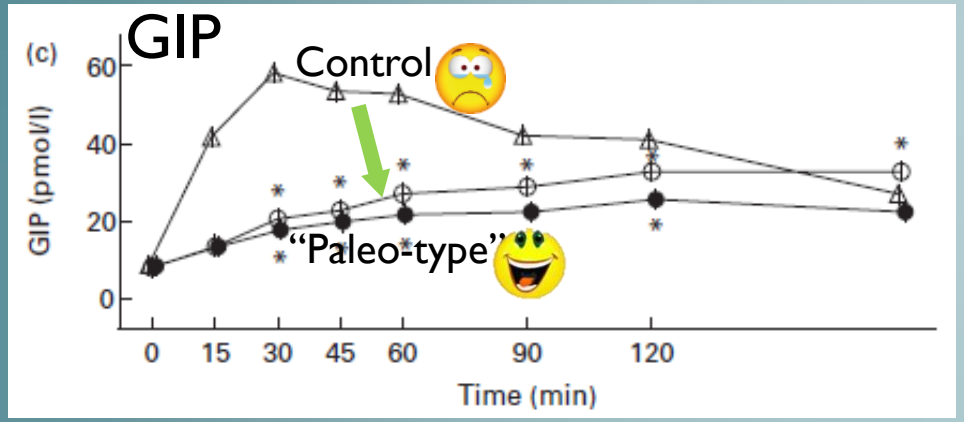

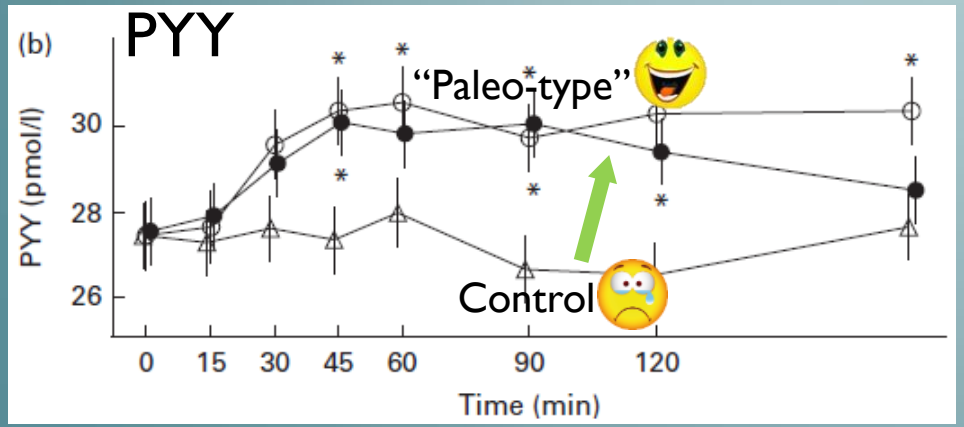

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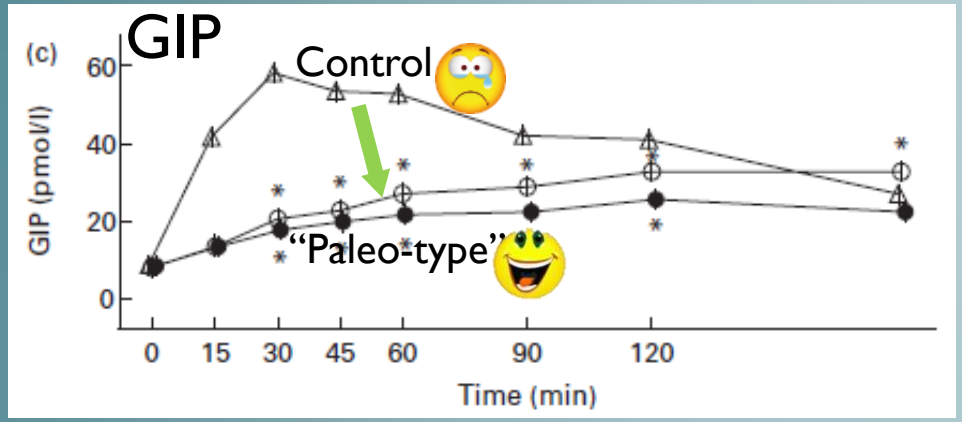

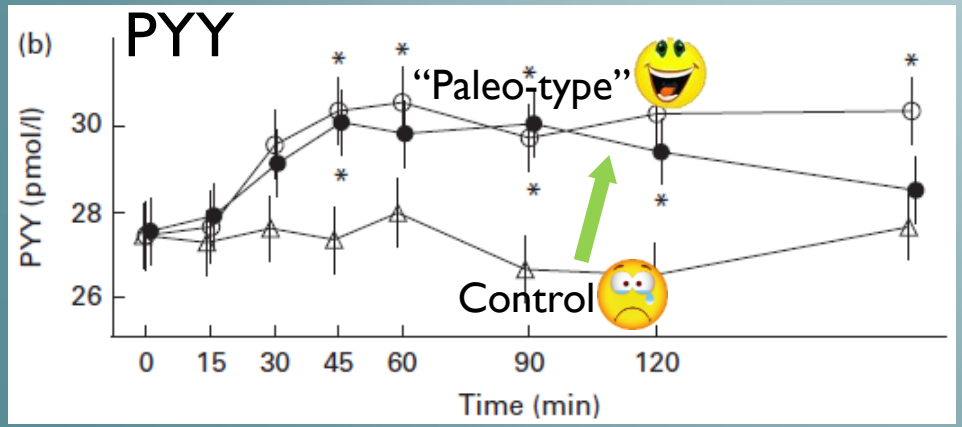

➢**Other studies show that cellular *structure* of food is key**

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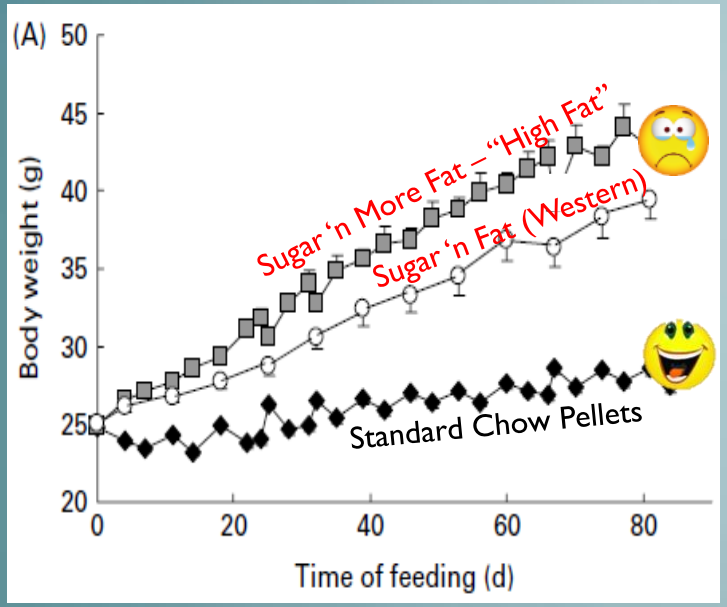

Diet-induced obesity in ad libitum-fed mice: Food texture overrides the effect of macronutrient composition *The British journal of nutrition* · *August 2012*

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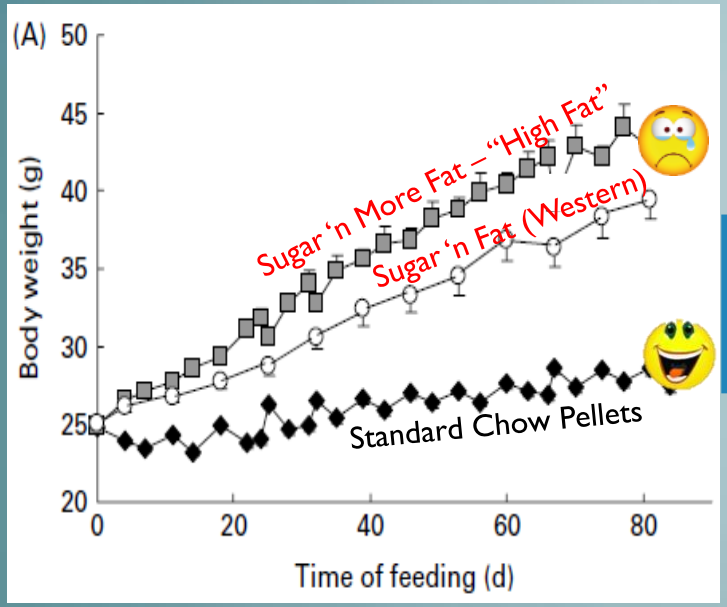

Grind up **each** diet?

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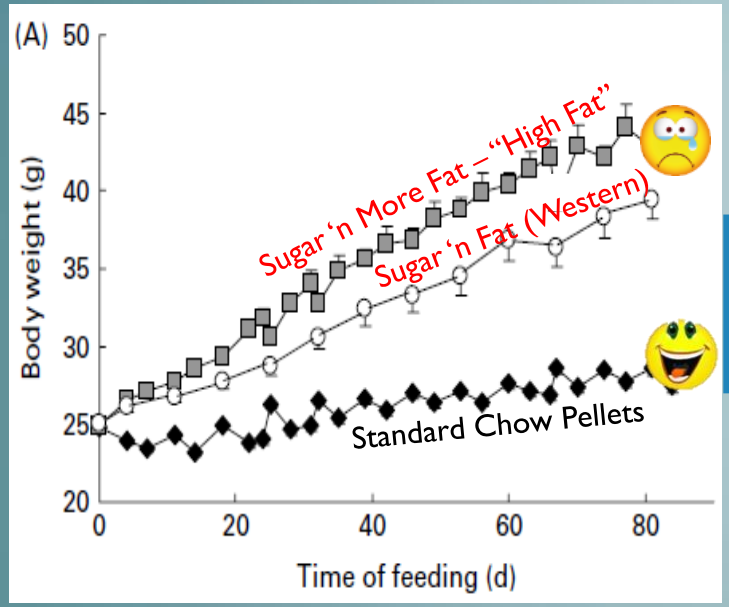
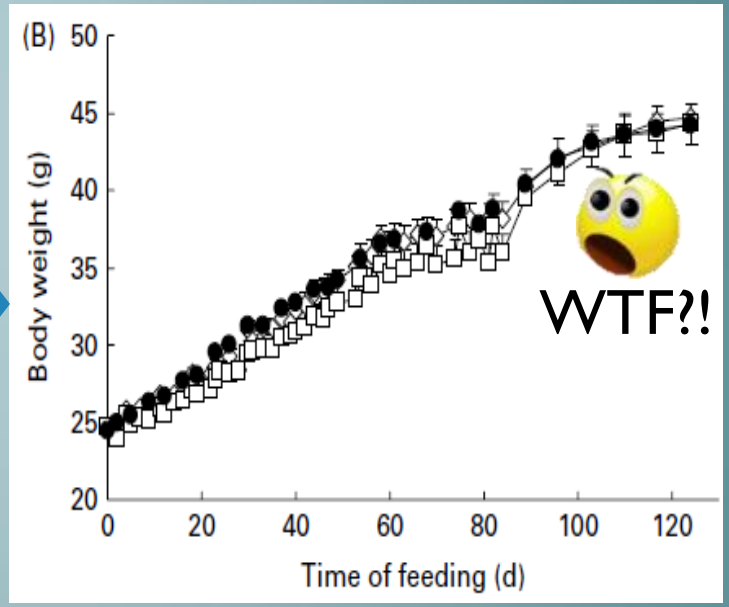
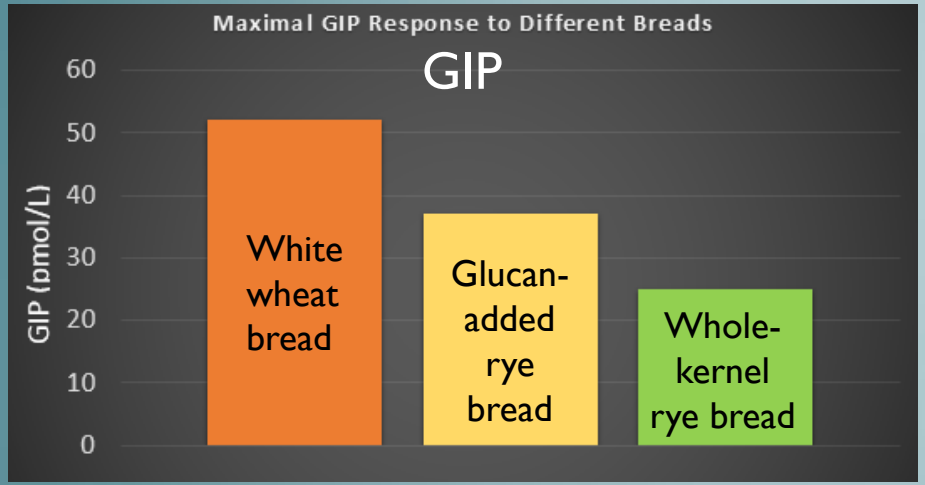


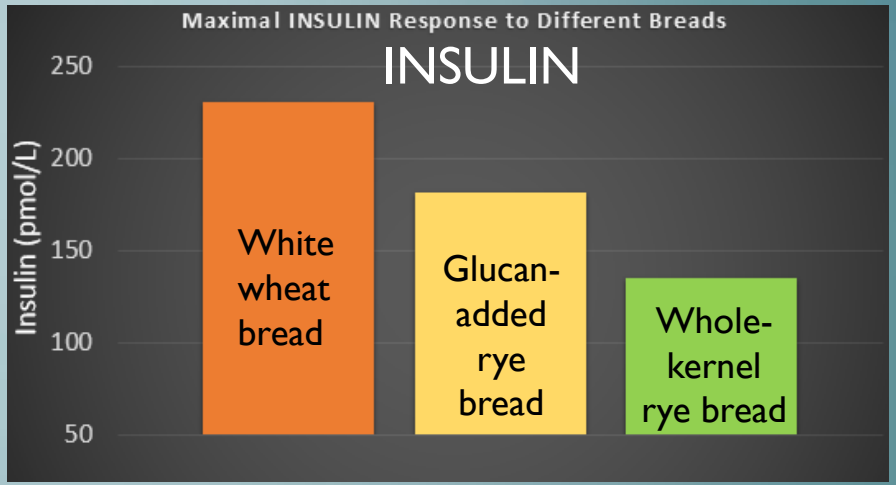
Grind up **each** diet?



Diet-induced obesity in ad libitum-fed mice: Food texture overrides the effect of macronutrient composition *The British journal of nutrition* · *August 2012*

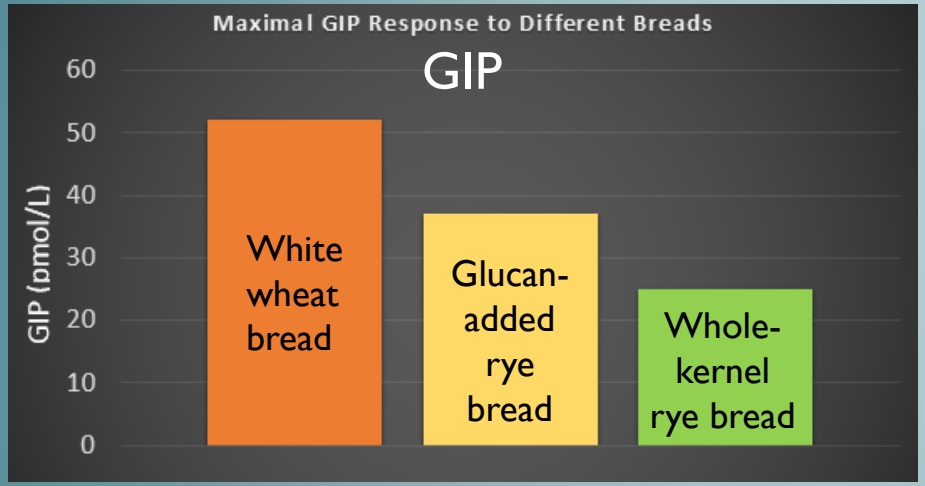
Refined Grains make FAT Humans?

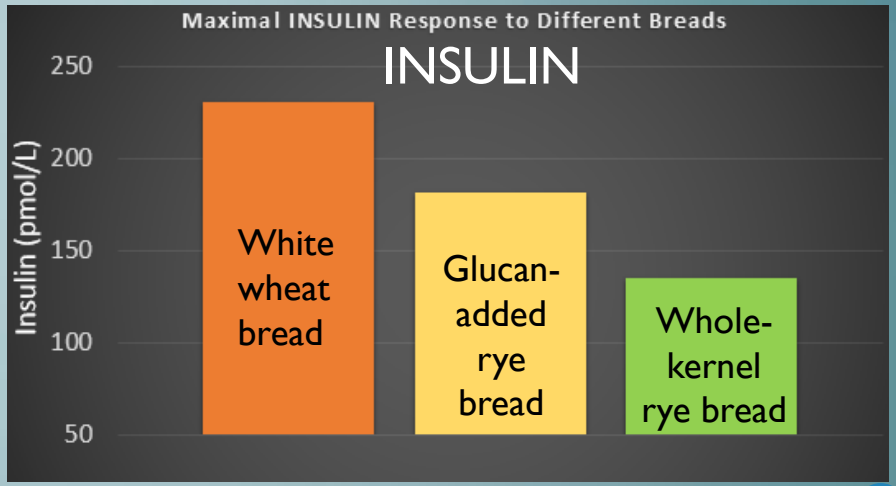




Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects *Am J Clin Nutr 2002;75:254–62*

Refined Grains make FAT Humans?

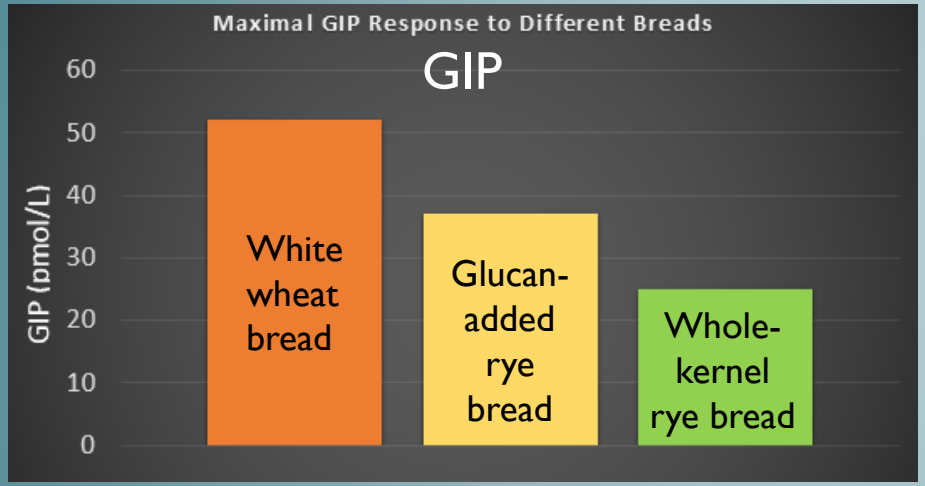


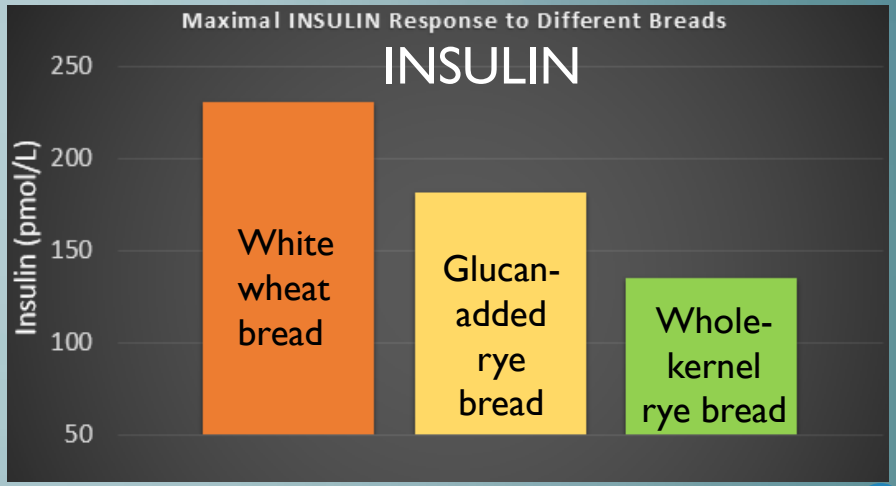


- **It wasn't the "fiber".**
- **It wasn't the "gastric emptying" effect.**

Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects *Am J Clin Nutr 2002;75:254–62*

Refined Grains make FAT Humans?

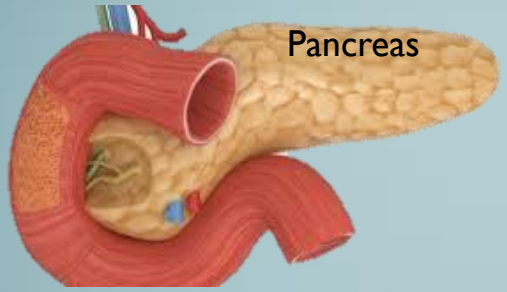


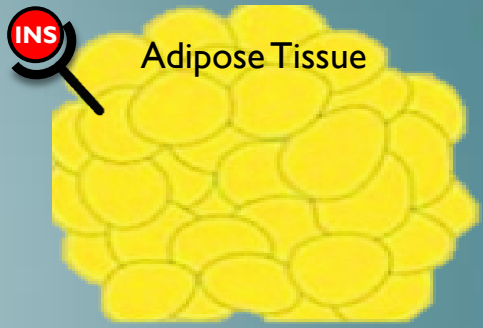


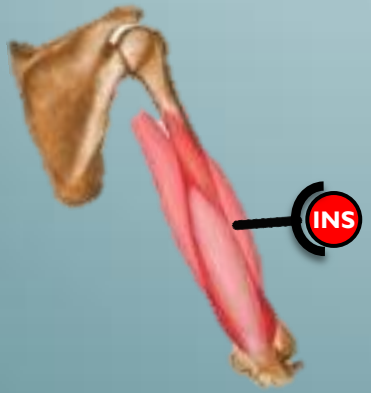
- **It wasn't the "fiber".**
- **It wasn't the "gastric emptying" effect.**
- **It was simply the cellular structure of the food particles.**

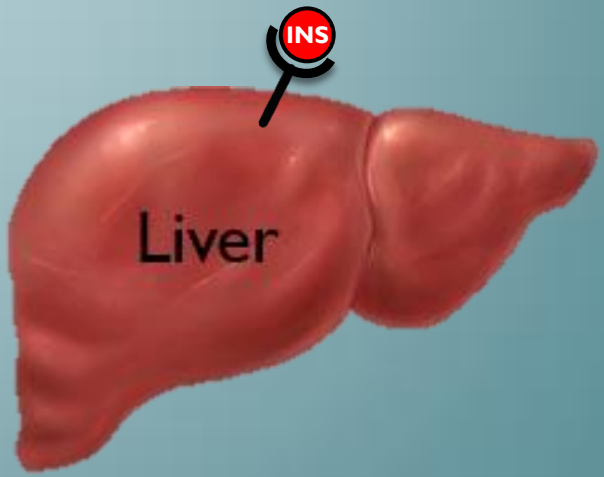
Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects *Am J Clin Nutr 2002;75:254–62*

The Insulin Resistance / Hyperinsulinemia Journey

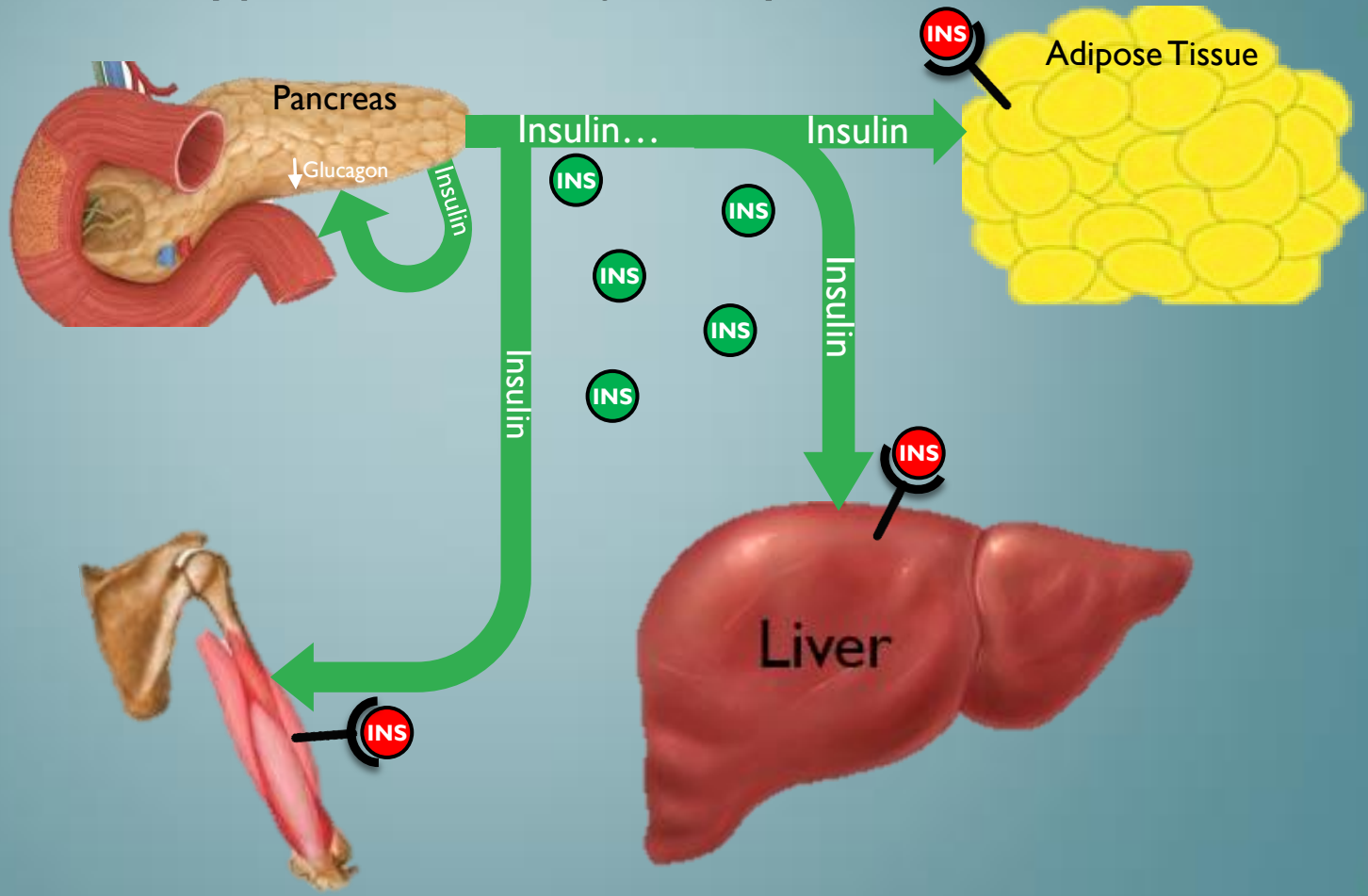




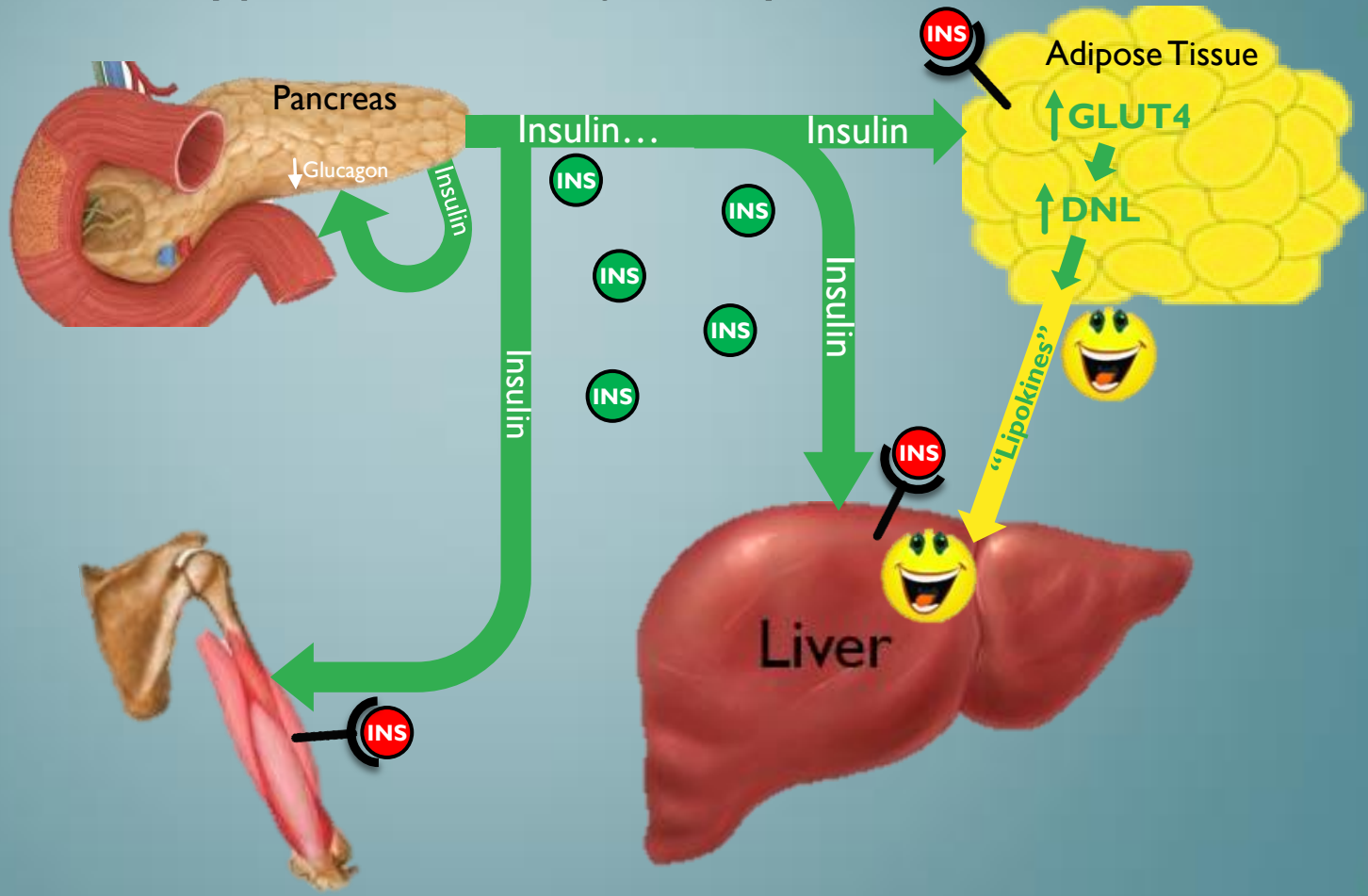




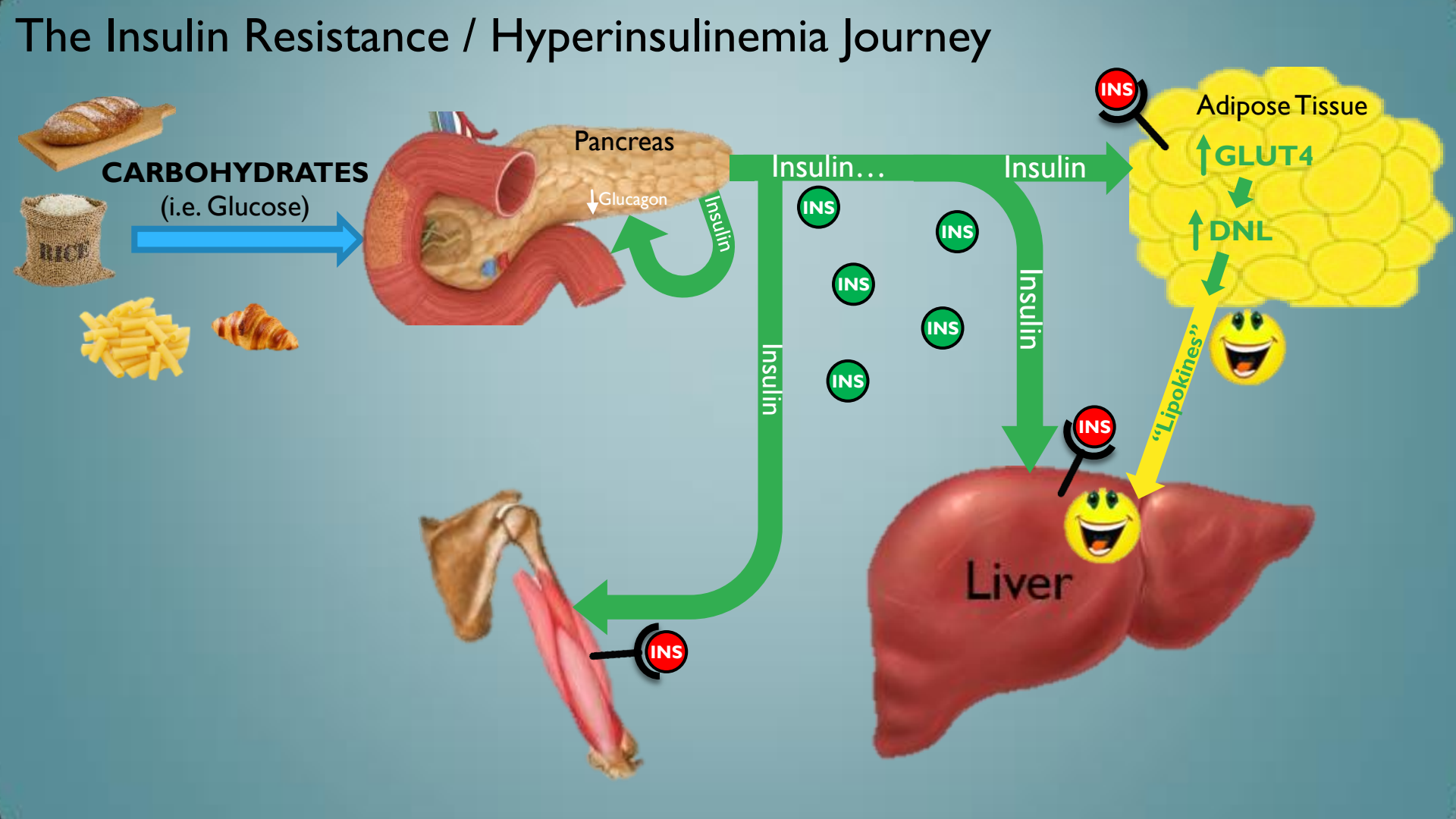
The Insulin Resistance / Hyperinsulinemia Journey



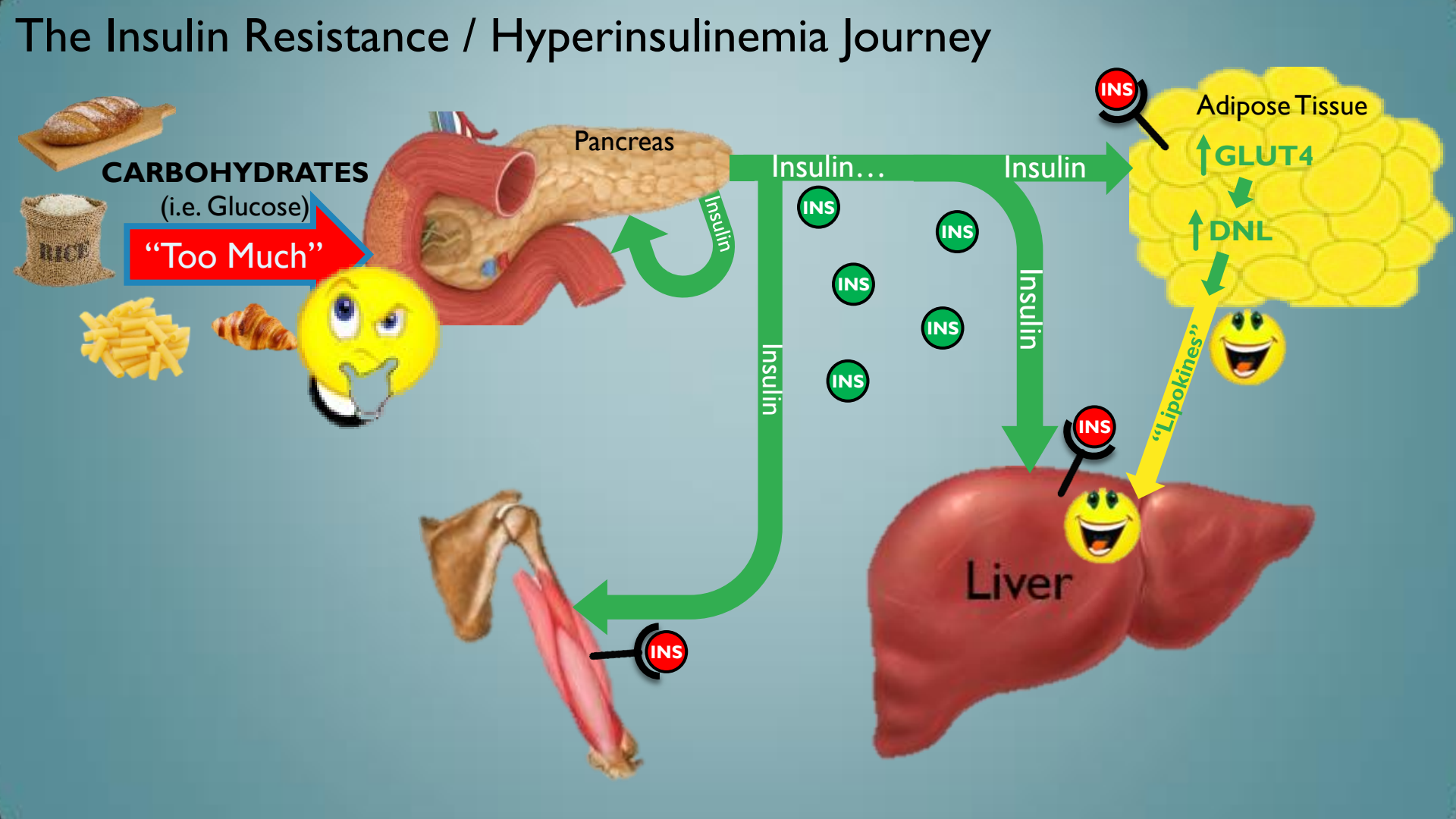
The Insulin Resistance / Hyperinsulinemia Journey



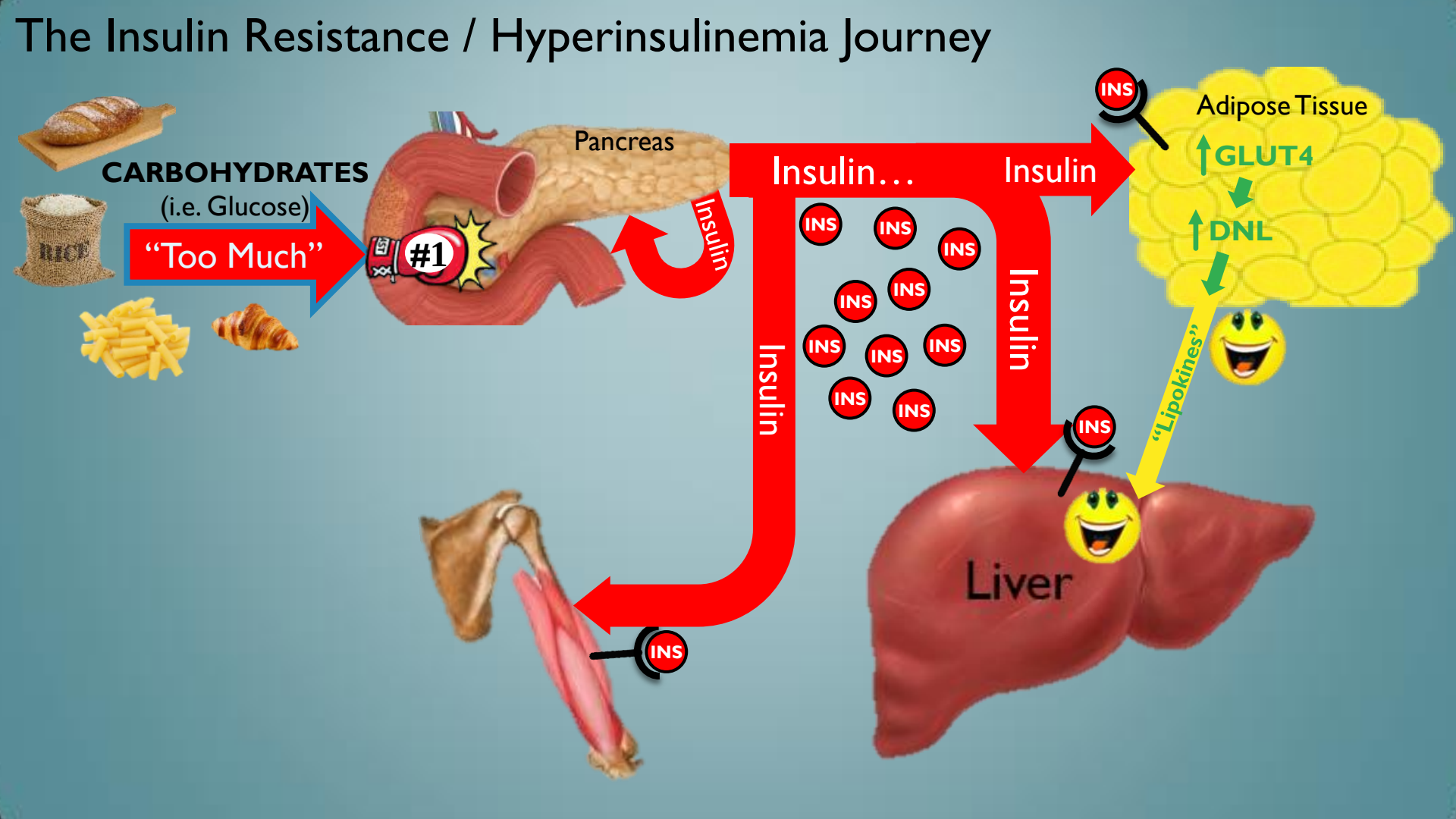
The Insulin Resistance / Hyperinsulinemia Journey



The Insulin Resistance / Hyperinsulinemia Journey



The Insulin Resistance / Hyperinsulinemia Journey



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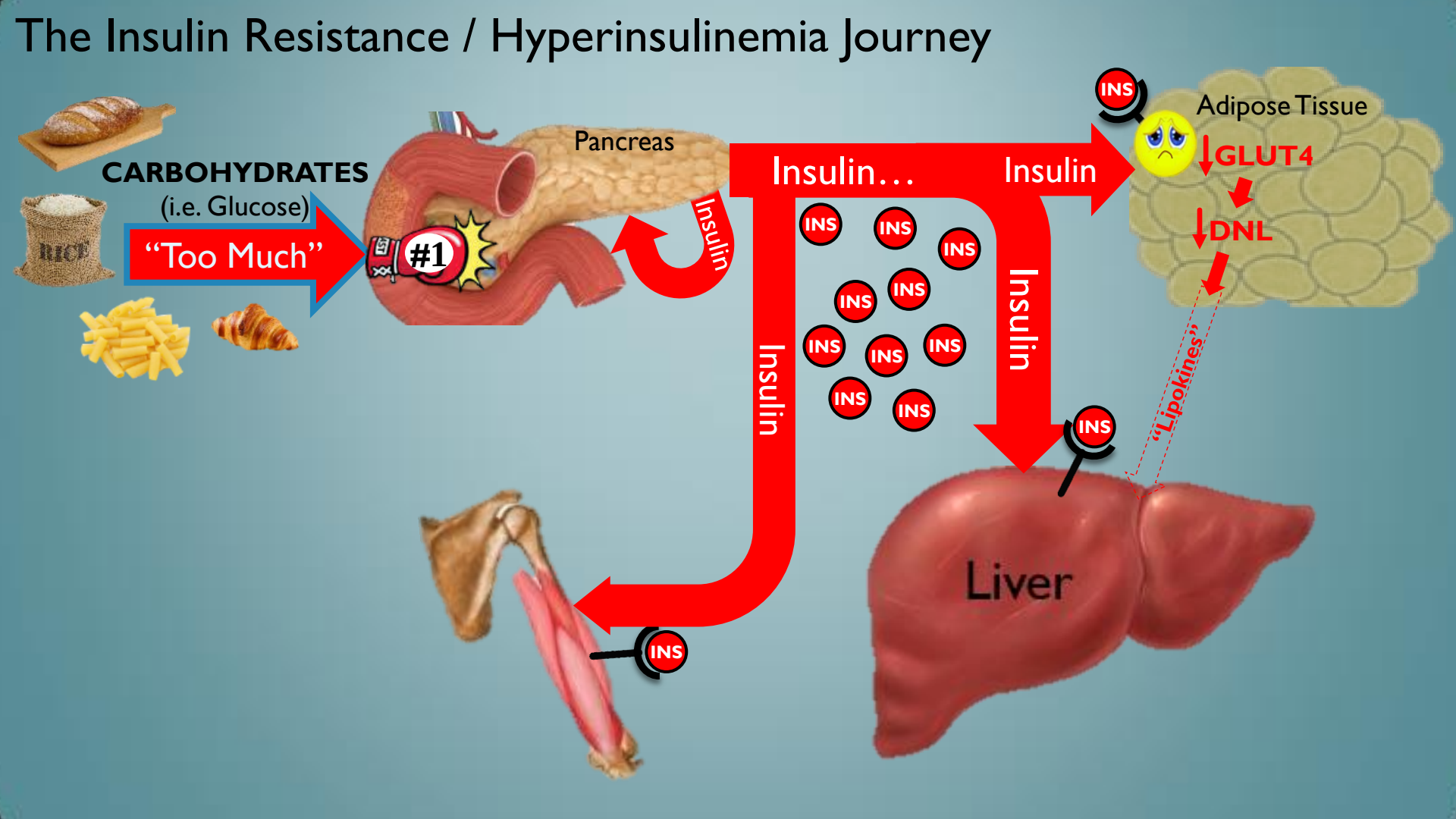
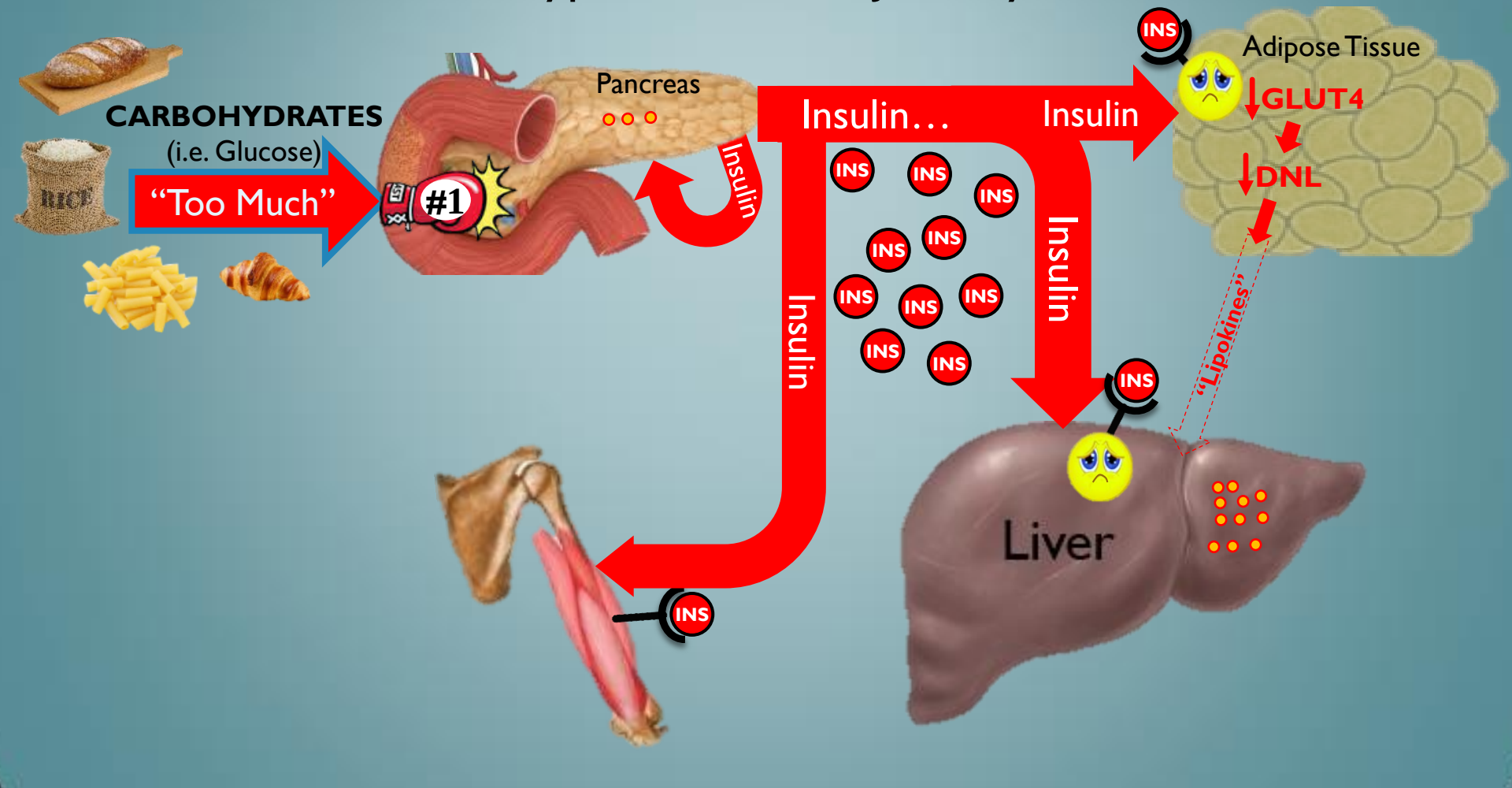
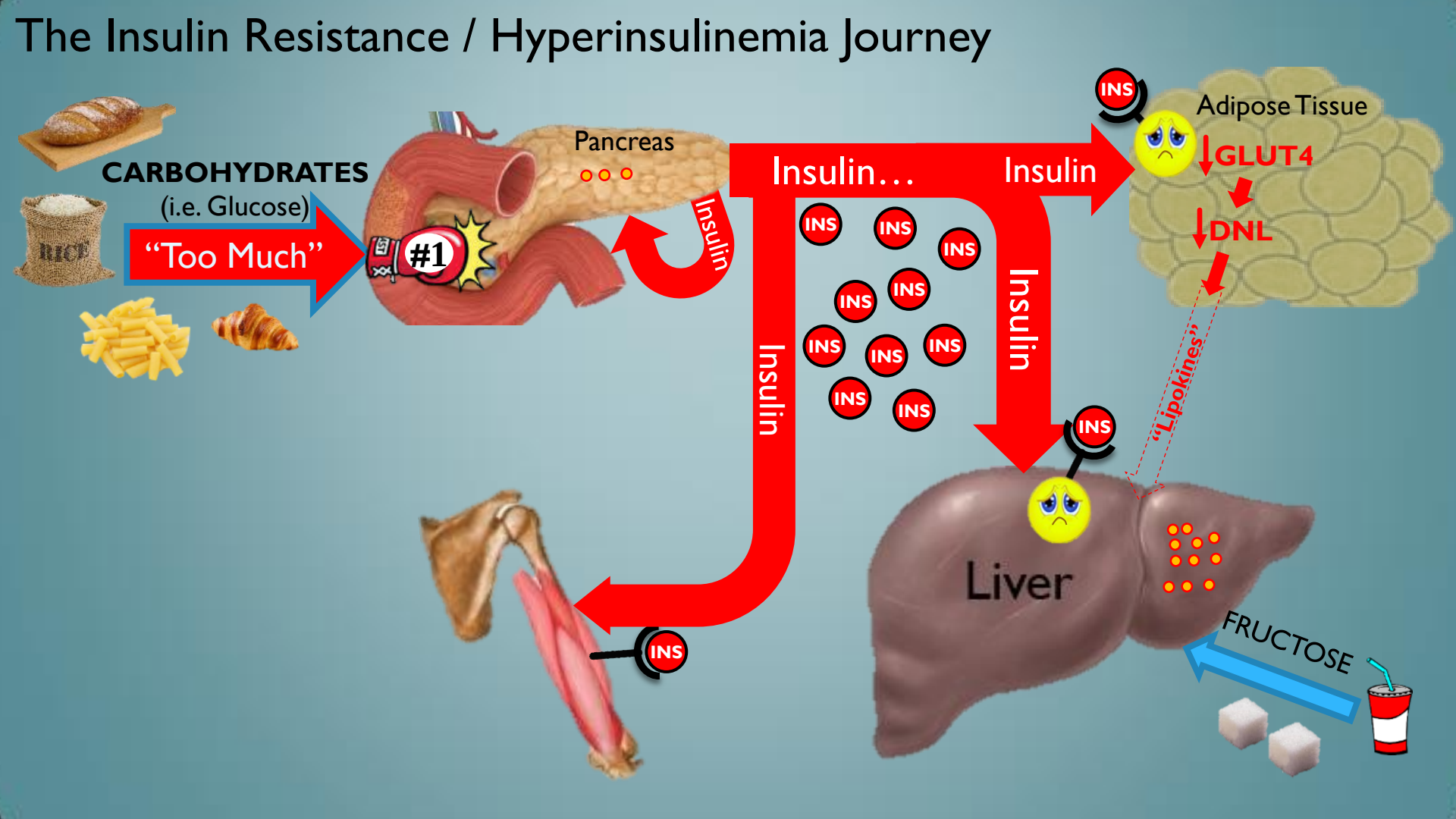


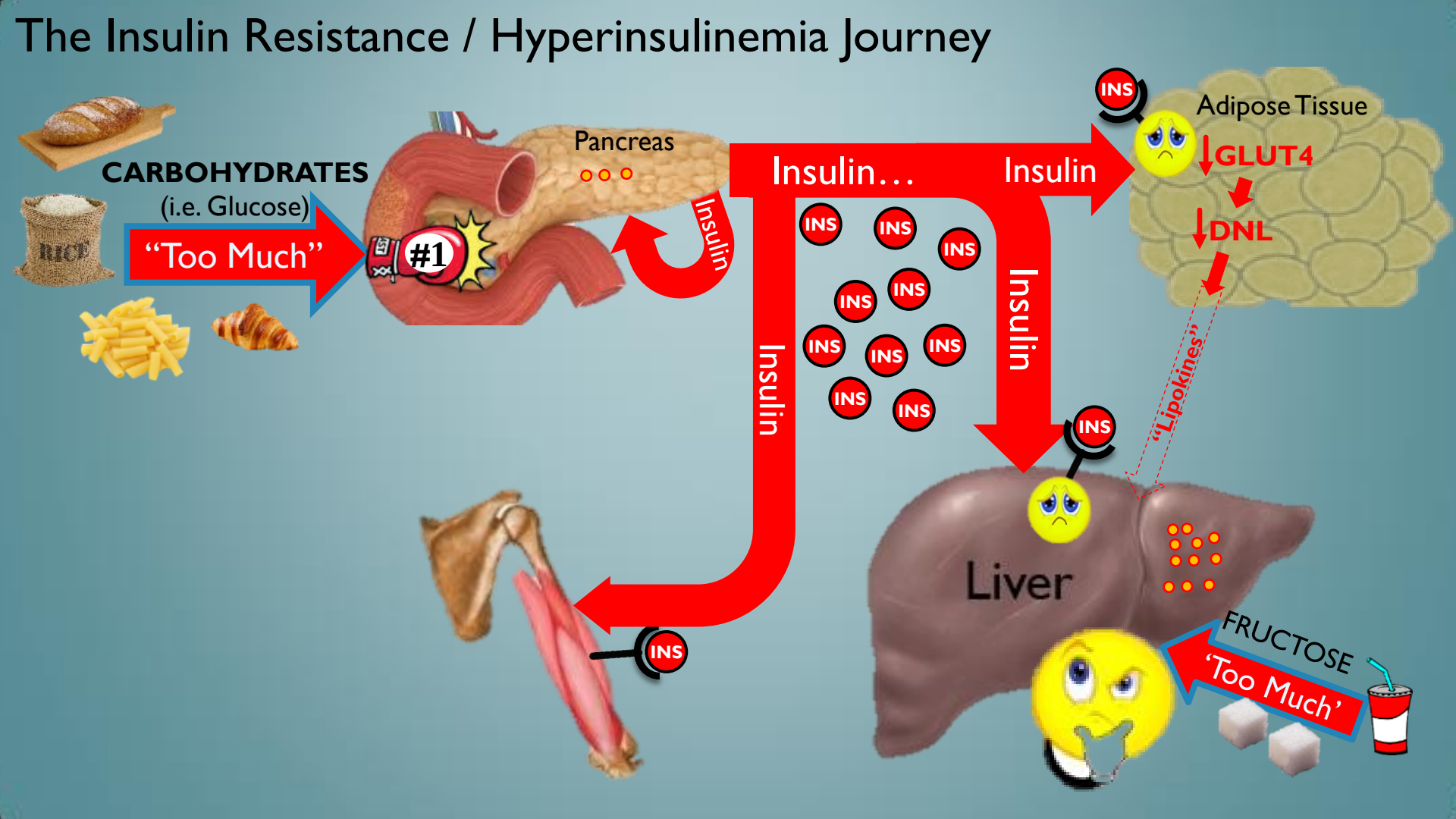
The Insulin Resistance / Hyperinsulinemia Journey



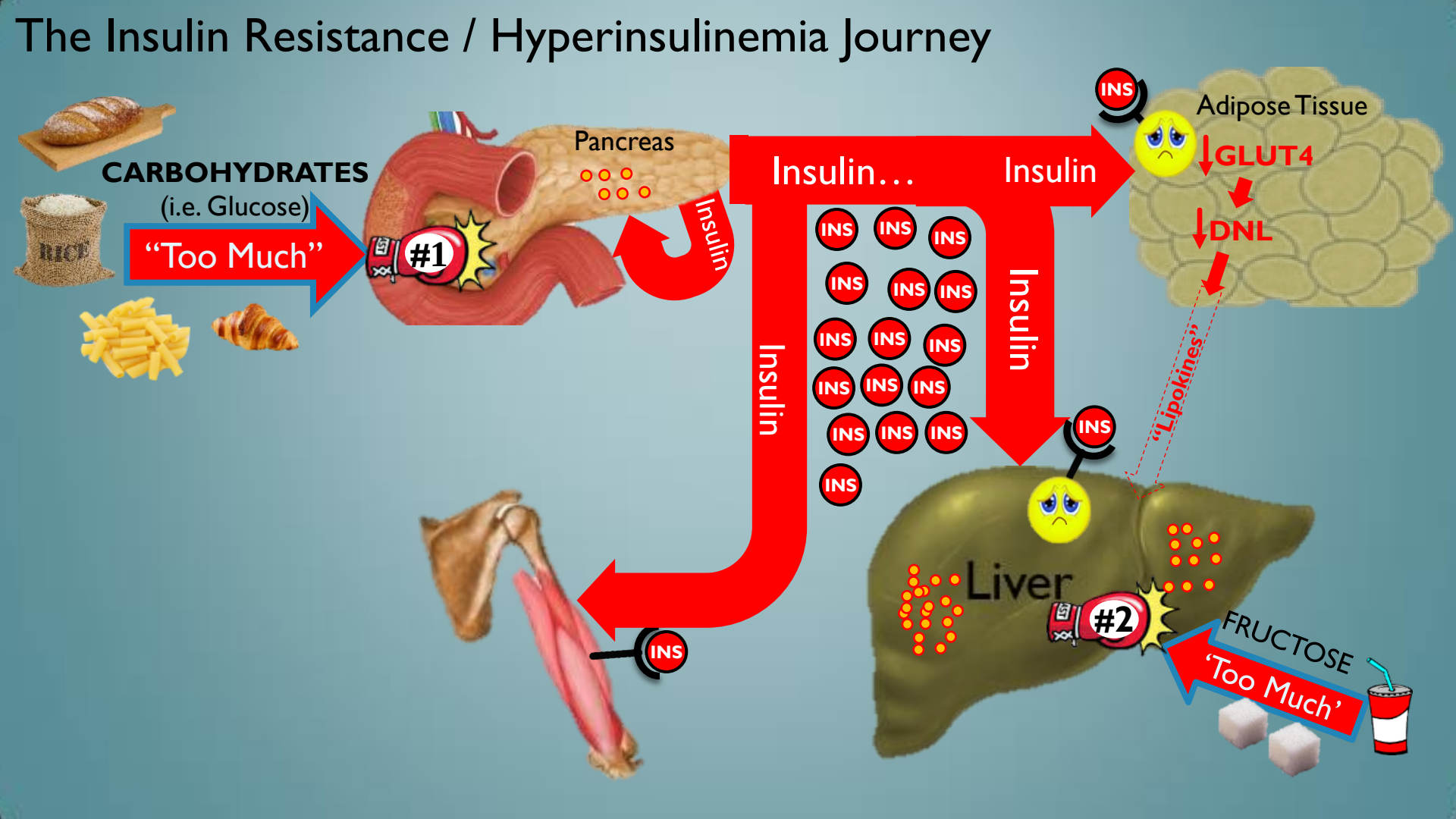
The Insulin Resistance / Hyperinsulinemia Journey



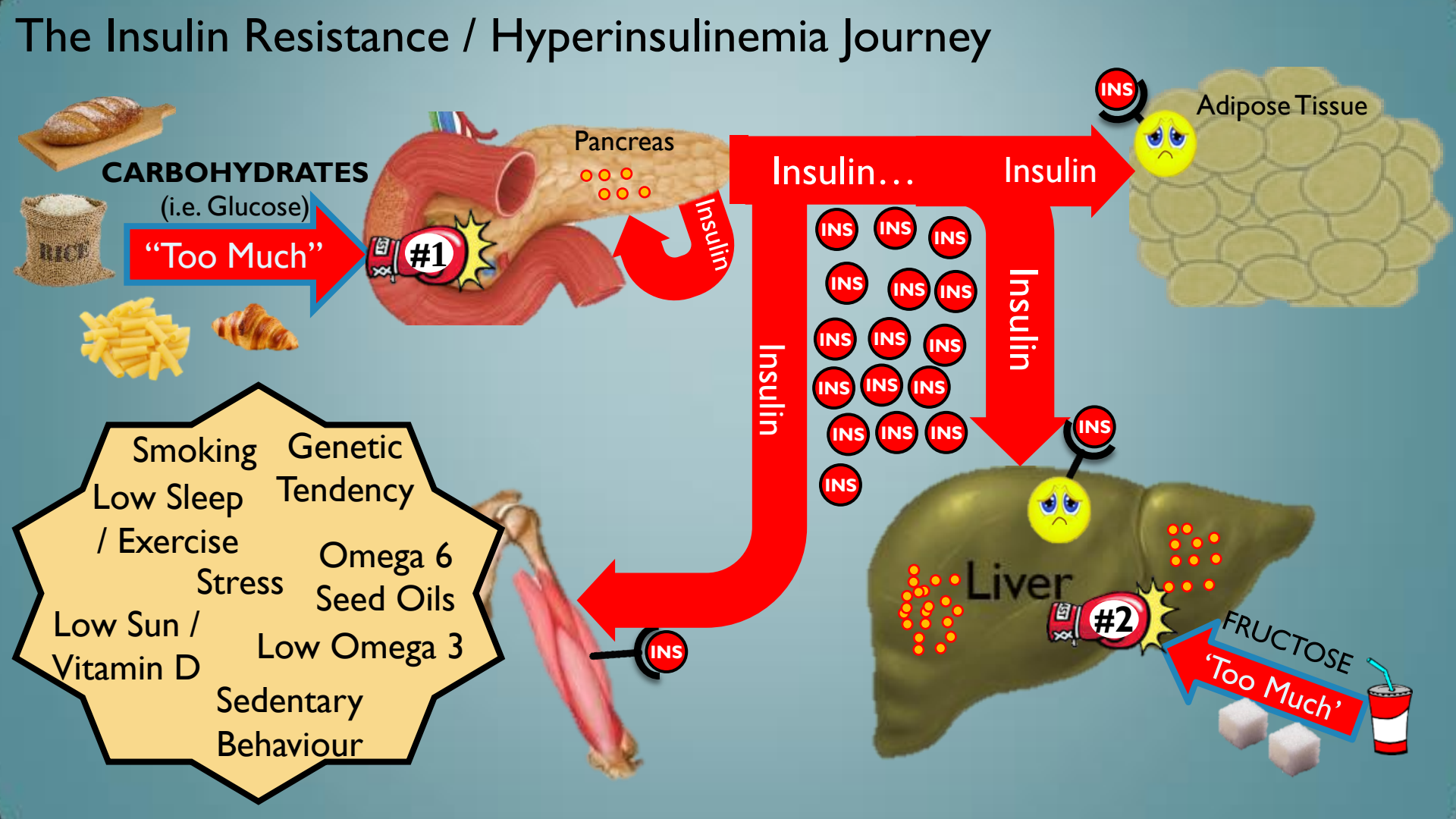
The Insulin Resistance / Hyperinsulinemia Journey



The Insulin Resistance / Hyperinsulinemia Journey

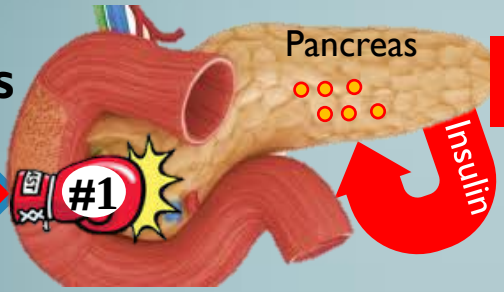


The Insulin Resistance / Hyperinsulinemia Journey



The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES
(i.e. Glucose)
"Too Much"



Pancreas

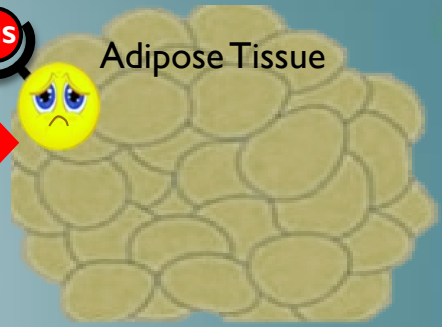
Insulin

Insulin…

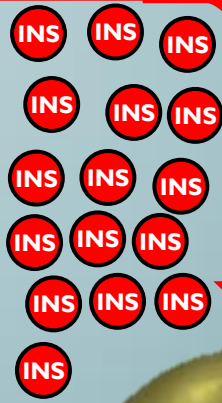
Insulin

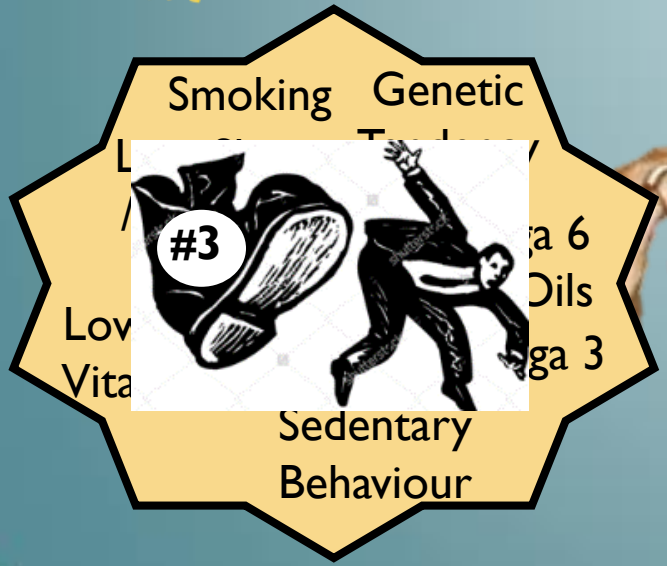
Insulin

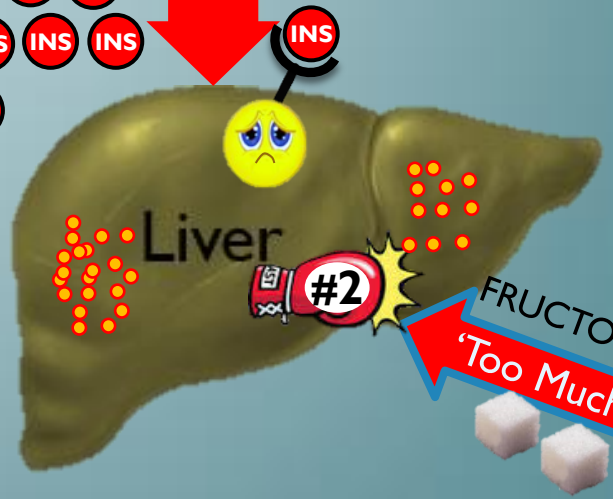
Insulin



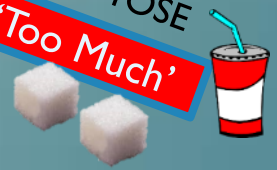
Adipose Tissue





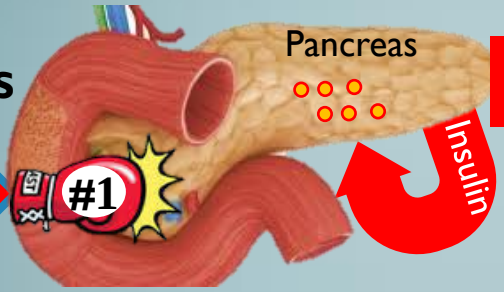


FRUCTOSE
'Too Much'



The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES
(i.e. Glucose)
"Too Much"

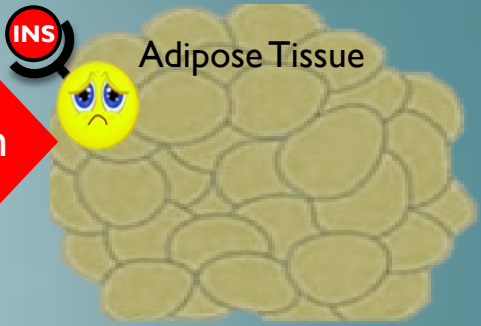


Pancreas

Insulin

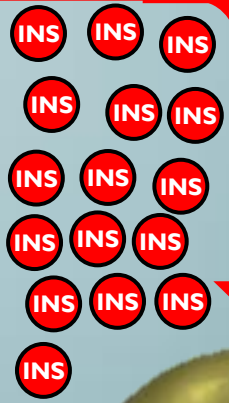
Insulin…

Insulin

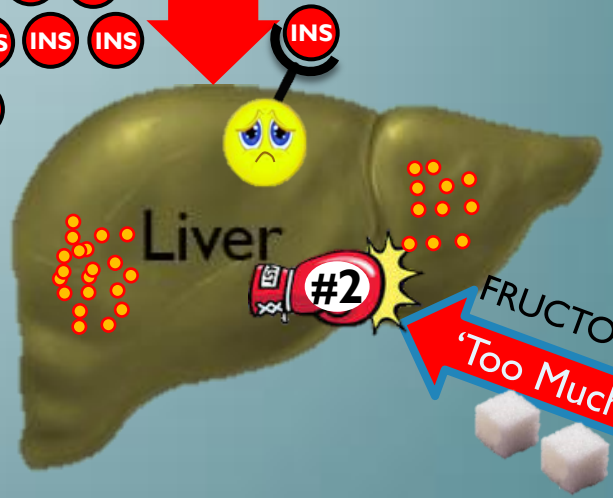


Adipose Tissue

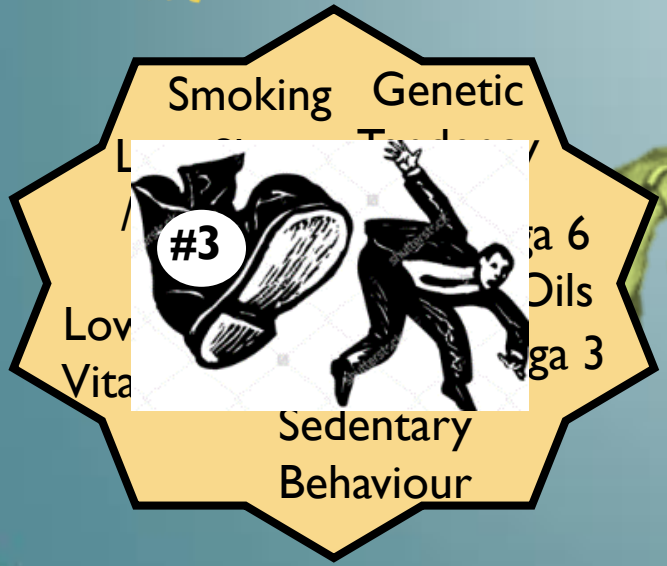
Insulin



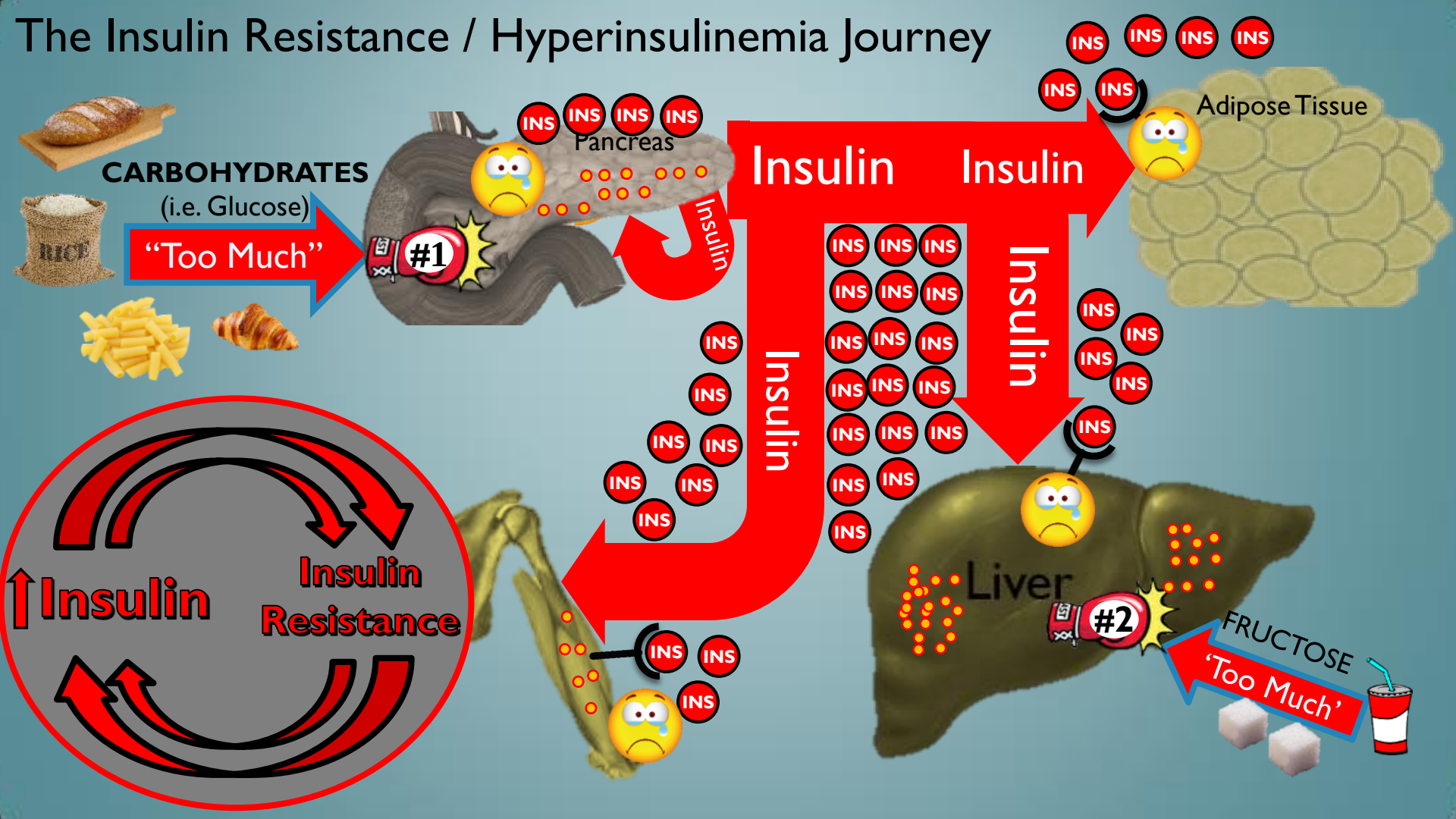
Insulin

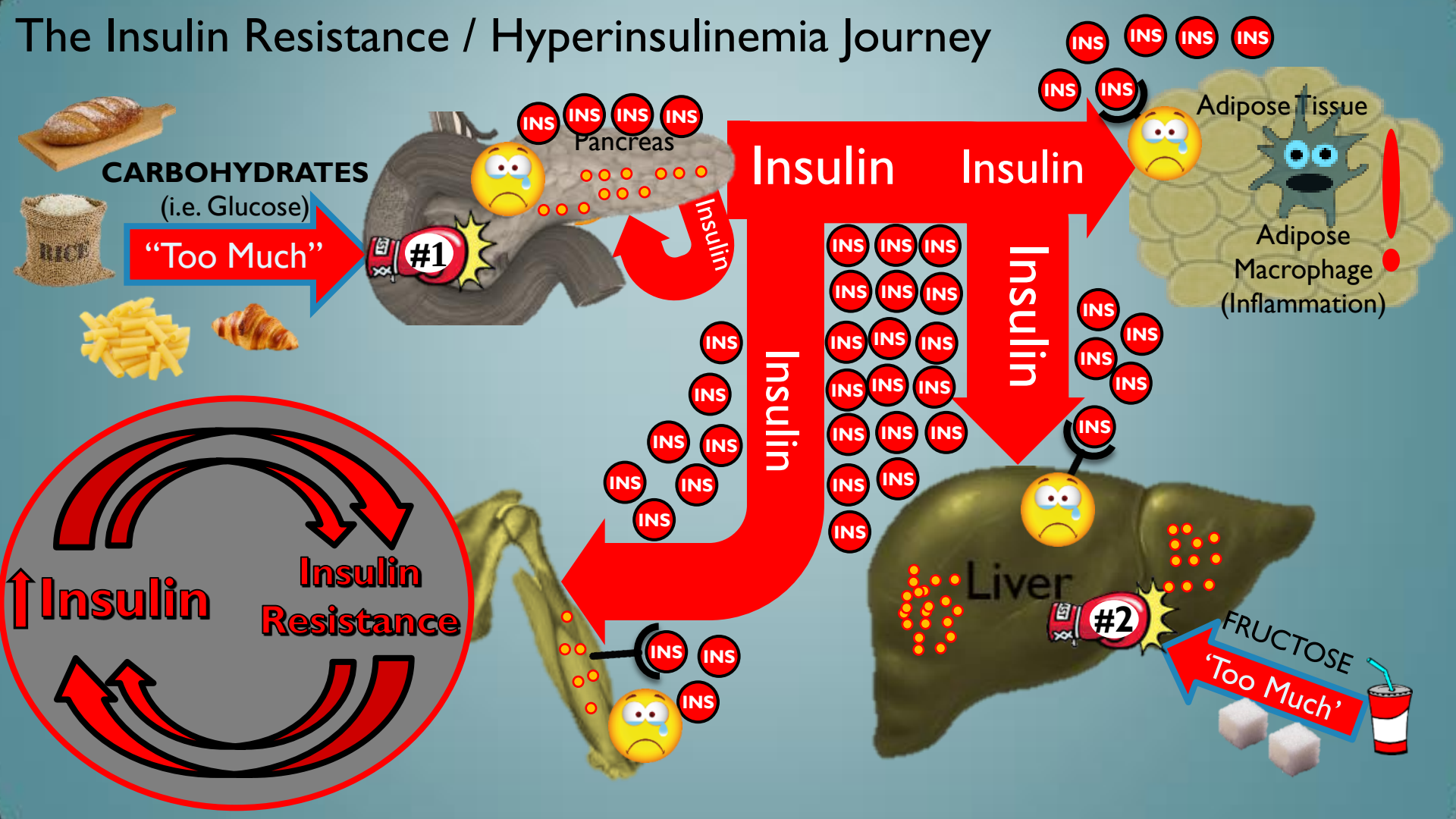


FRUCTOSE
'Too Much'

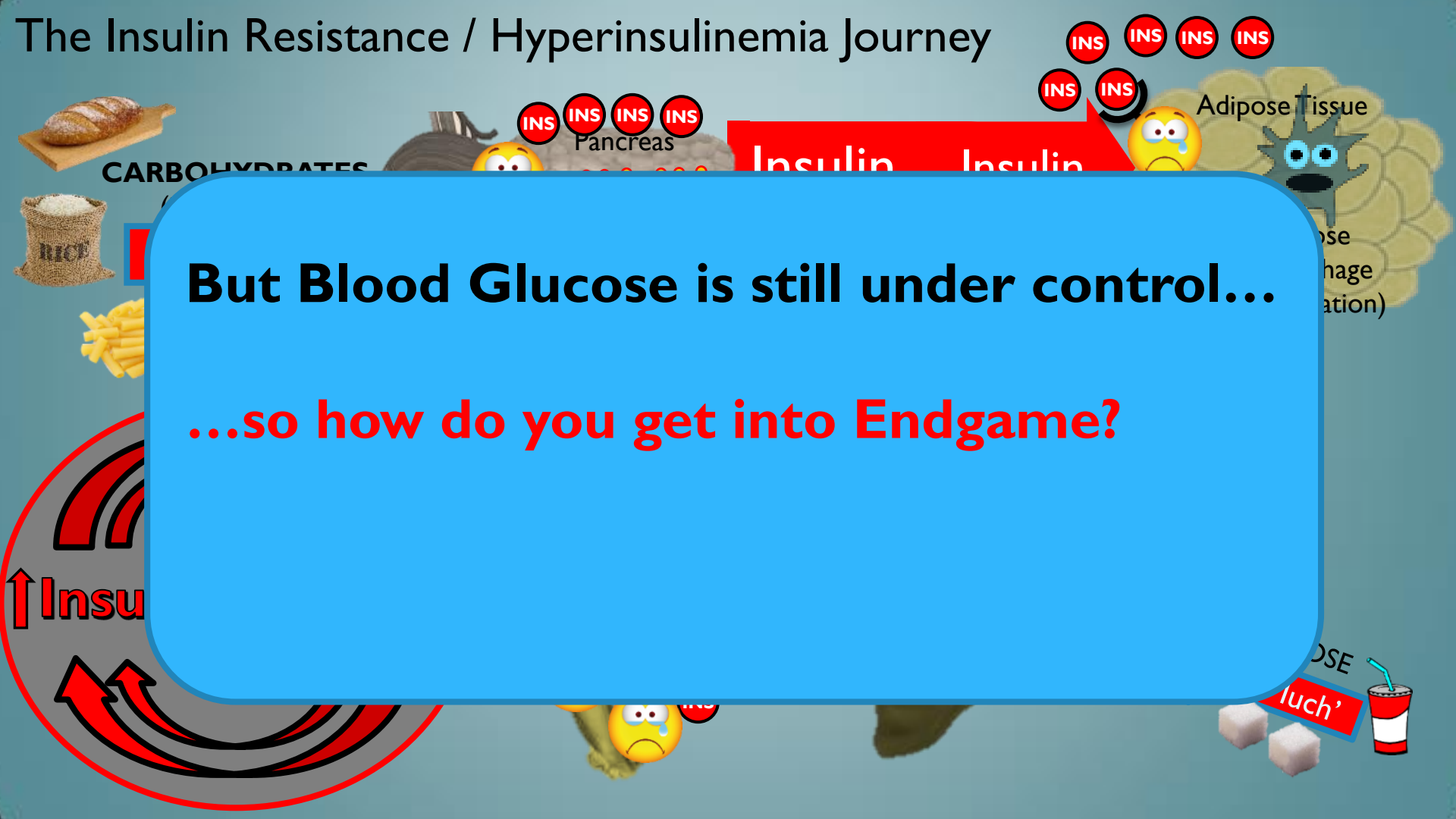


The Insulin Resistance / Hyperinsulinemia Journey




The Insulin Resistance / Hyperinsulinemia Journey
CARBOHYDRATES
(i.e. Glucose)
"Too Much"
#1
Pancreas
Insulin
Insulin
Insulin
Insulin
Adipose Tissue
Adipose Macrophage (Inflammation)
Liver
#2
FRUCTOSE
'Too Much'
Insulin
Insulin Resistance

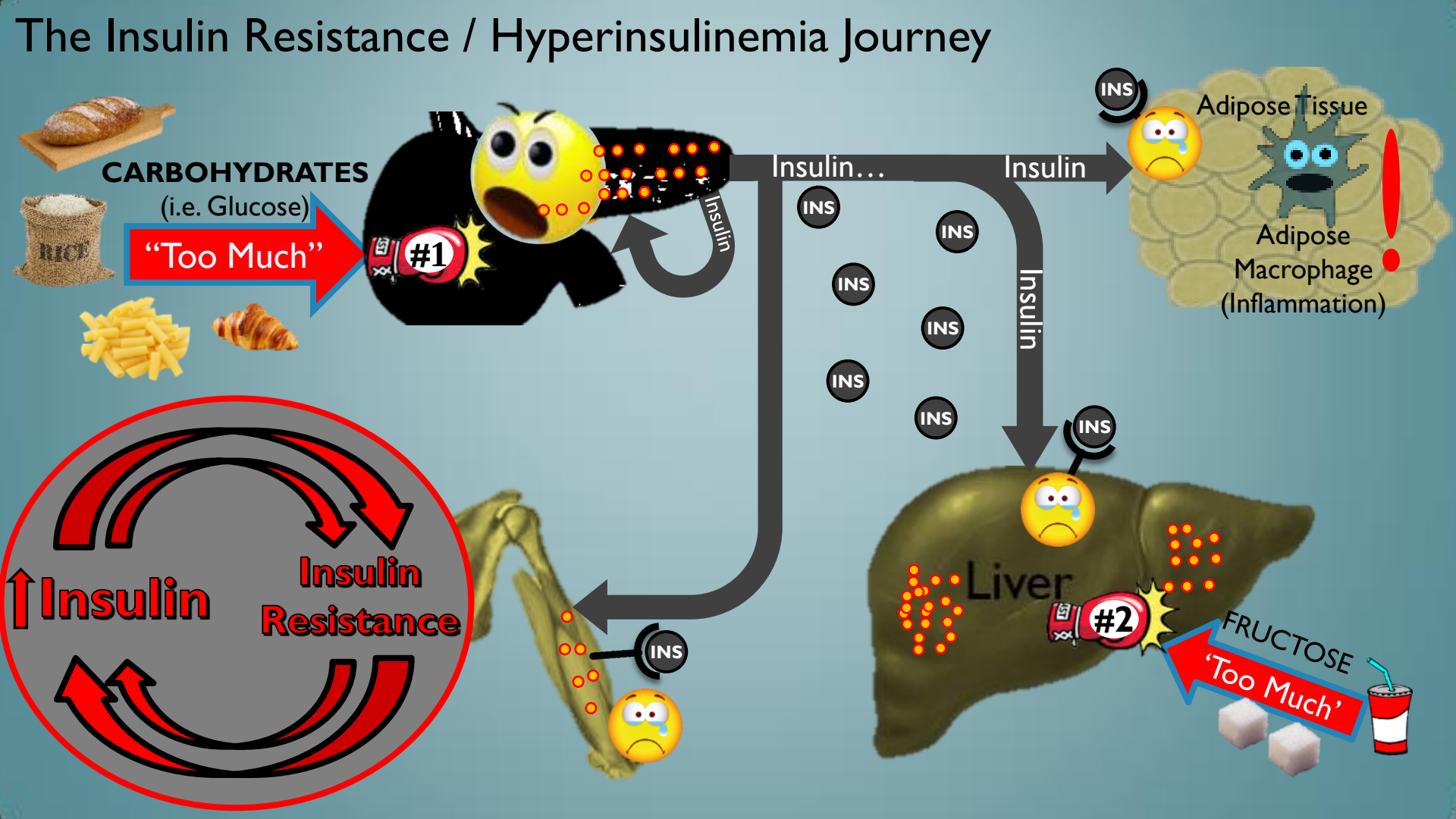
The Insulin Resistance / Hyperinsulinemia Journey



But Blood Glucose is still under control…

…so how do you get into Endgame?

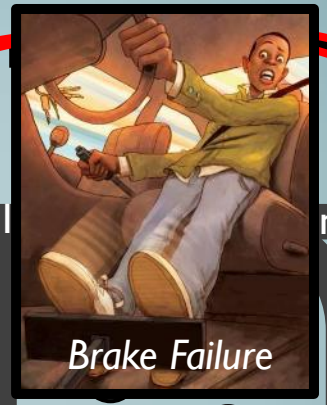
The Insulin Resistance / Hyperinsulinemia Journey



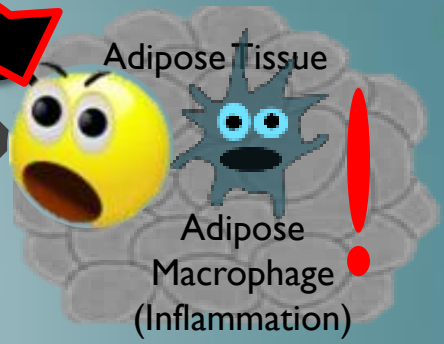
The Insulin Resistance / Hyperinsulinemia

CARBOHYDRATES
(i.e. Glucose)

"Too Much"



Insulin



Insulin

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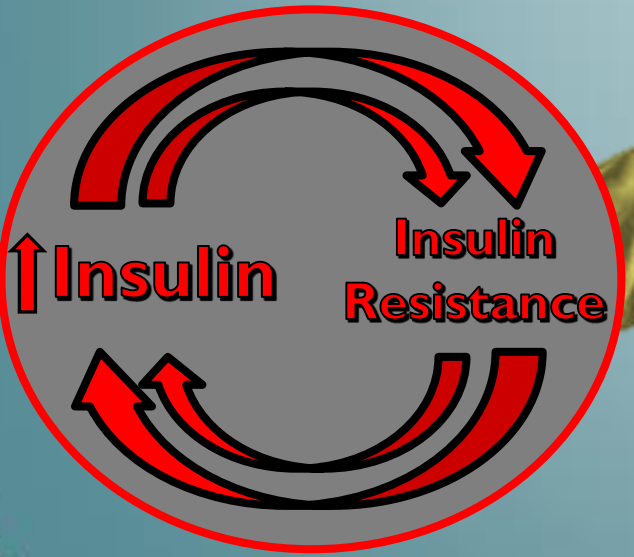
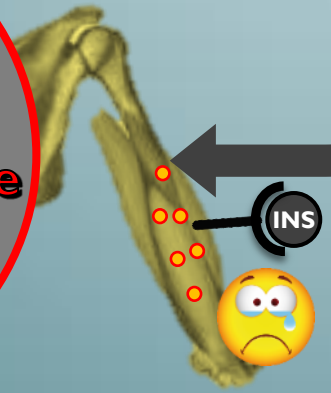
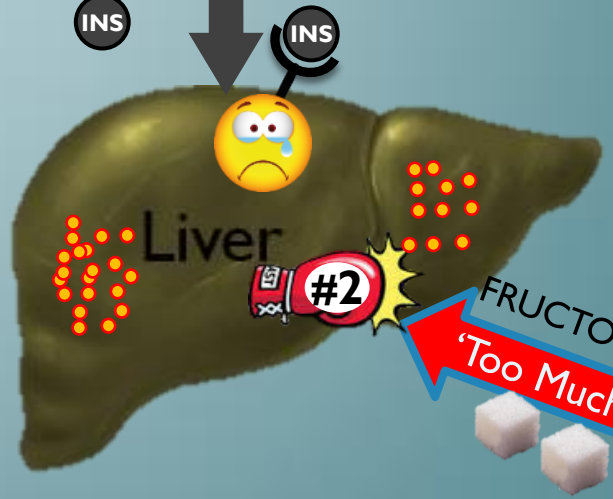
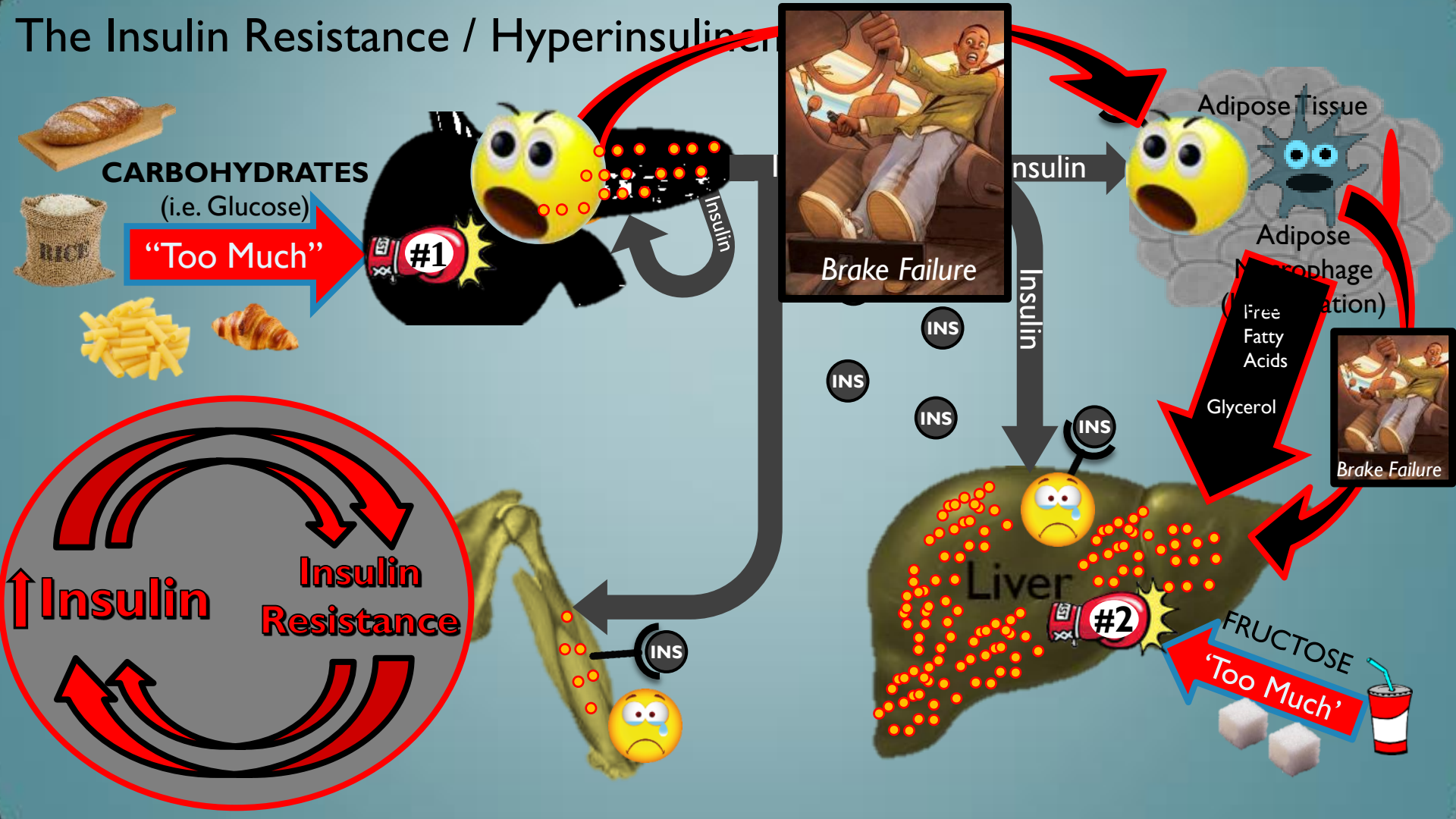
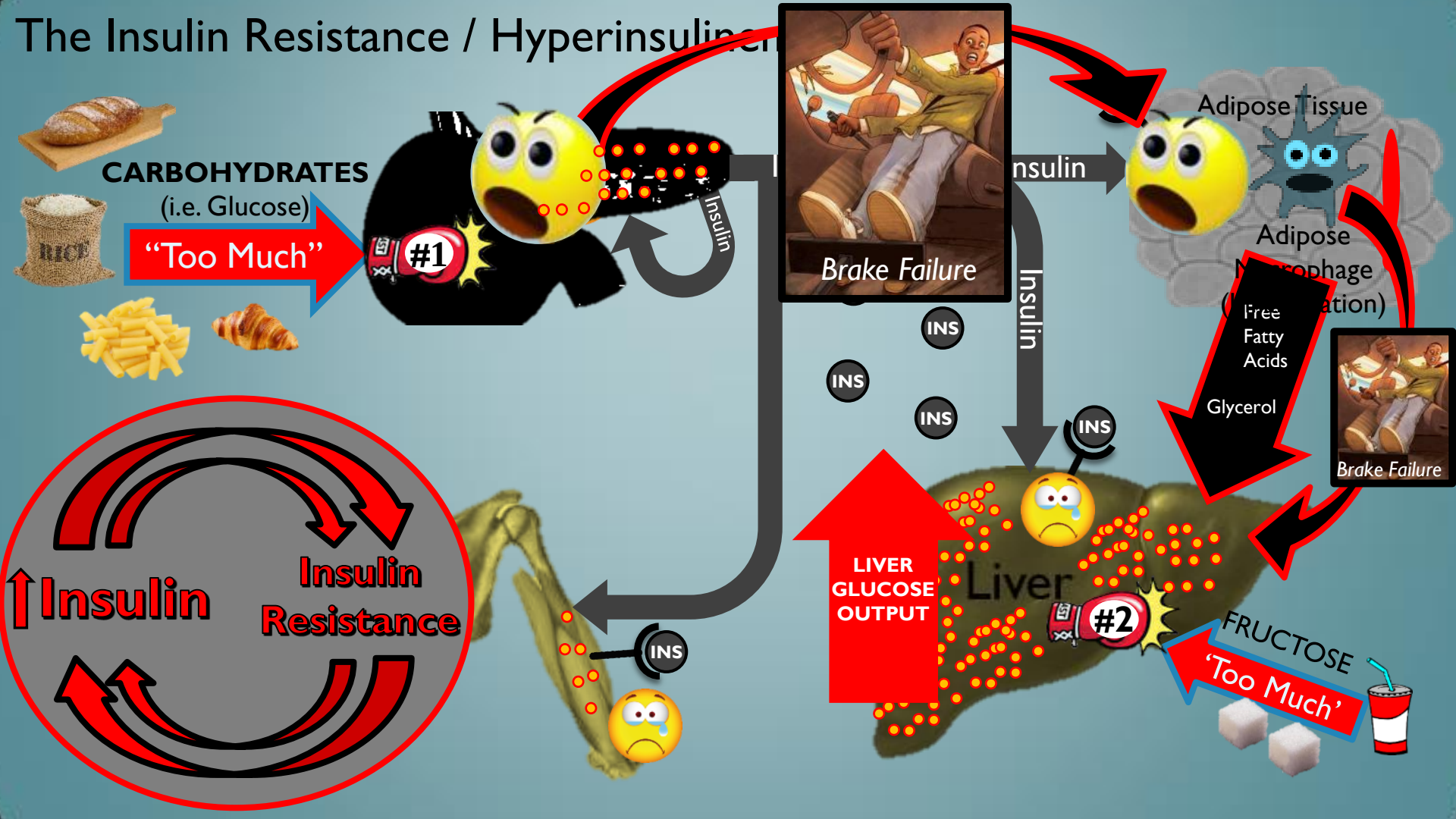







The Insulin Resistance / Hyperinsulinem
CARBOHYDRATES
(i.e. Glucose)
"Too Much"
#1
Insulin
Brake Failure
Insulin
Adipose Tissue
Adipose
Free
Fatty
Acids
Glycerol
Brake Failure
INS
INS
INS
INS
Insulin
Insulin
Resistance
Liver
#2
FRUCTOSE
'Too Much'

The Insulin Resistance / Hyperinsulinem



The Insulin Resistance / Hyperinsulinem

CARBOHYD

(i.e. Gluco

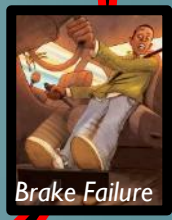
"Too Mu

Adipose Tissue

Adipose

Free
Fatty
Acids

Glycerol



Insulin

FRUCTOSE

'Too Much'

GAME OVER

INSERT INSULIN

TO CONTINUE

PART 3

The Power of the CAC Score

The Ultimate Test for CVD Presence

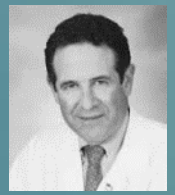
“We Stand on the Shoulder’s of Giants…”

Bruce Brundage
Cardiologist
Former Professor David Geffan
School of Medicine UCLA

Doug Boyd
Physicist, Inventor of CAC Technology
Former Professor of Radiology (Physics)
UCSF

Harvey S. Hecht
Cardiologist
Professor Mount Sinai Medical
Centre New York

John A. Rumberger
Cardiologist
Princeton Longevity Centre



Arthur Agatston
Cardiologist
Associate Professor of Medicine
University of Miami

Matthew J. Budoff
Cardiologist
Professor of Medicine UCLA

“We Stand on the Shoulder’s of Giants…”

Bruce Brundage
Cardiologist
Former Professor David Geffan
School of Medicine UCLA

Doug Boyd
Physicist, Inventor of CAC Technology
Former Professor of Radiology (Physics)
UCSF

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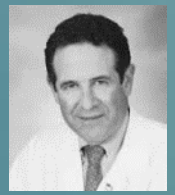

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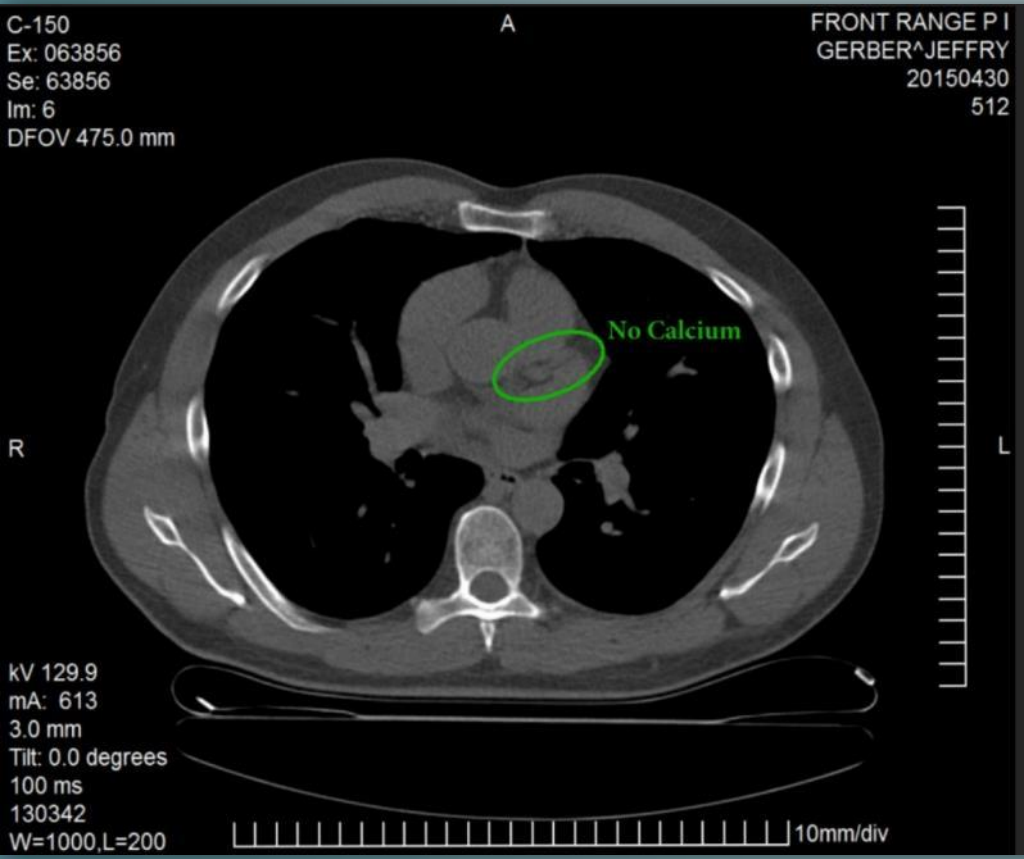
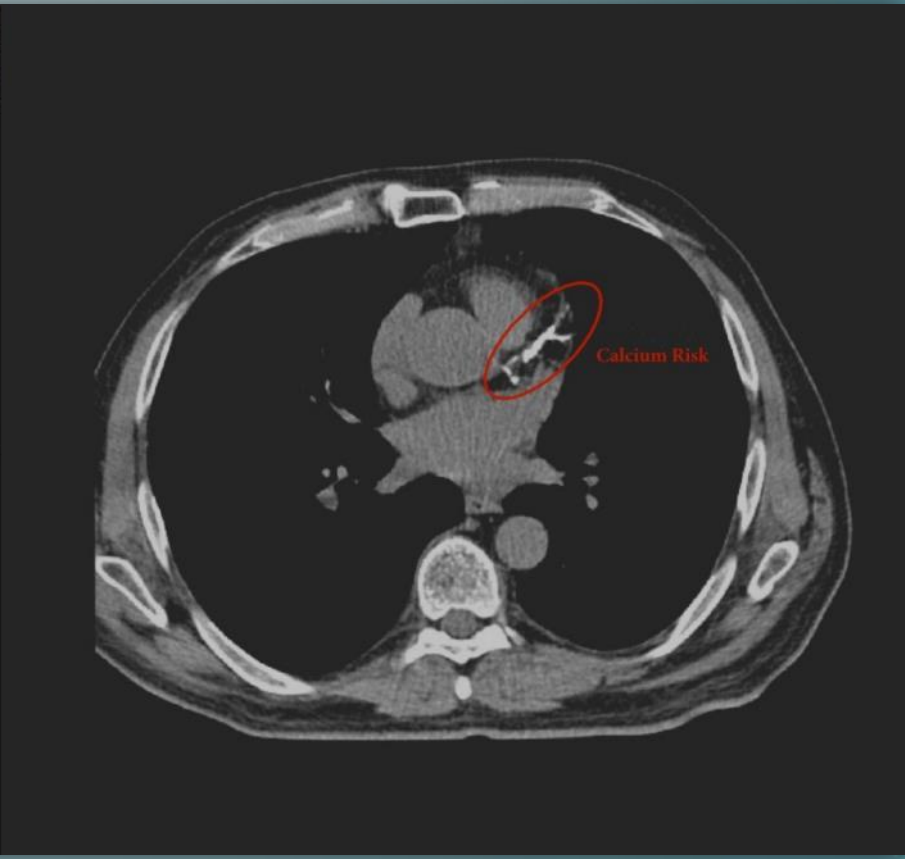
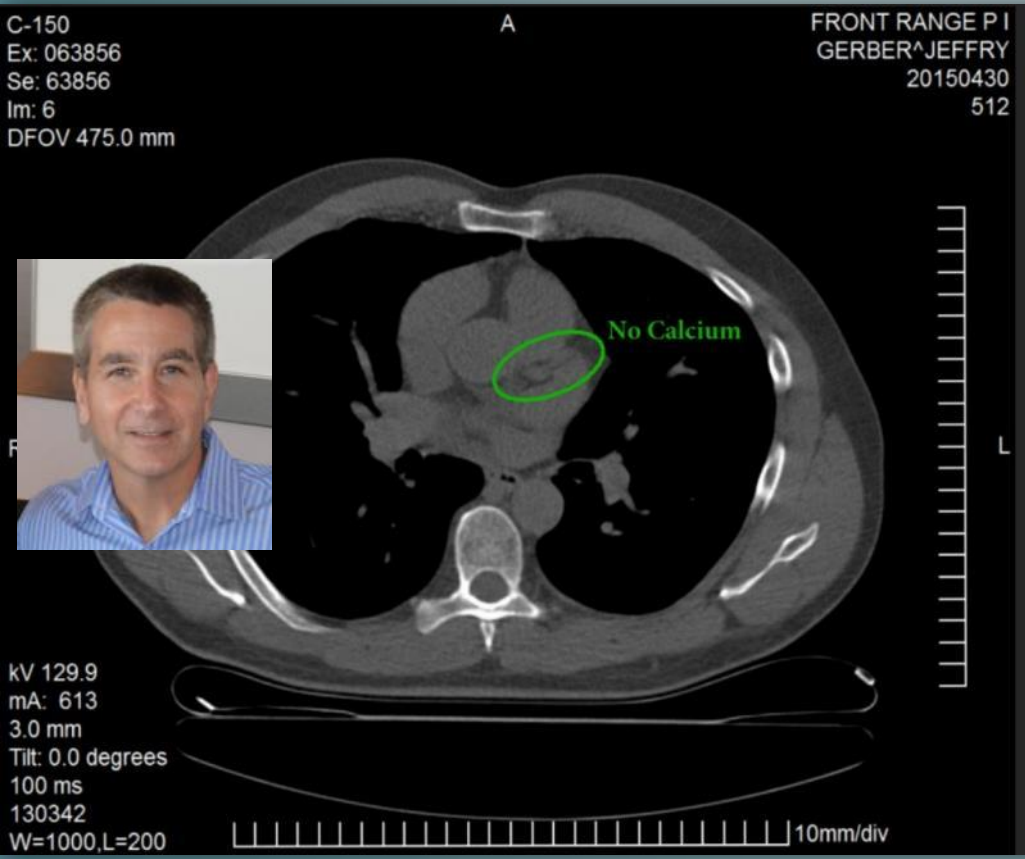
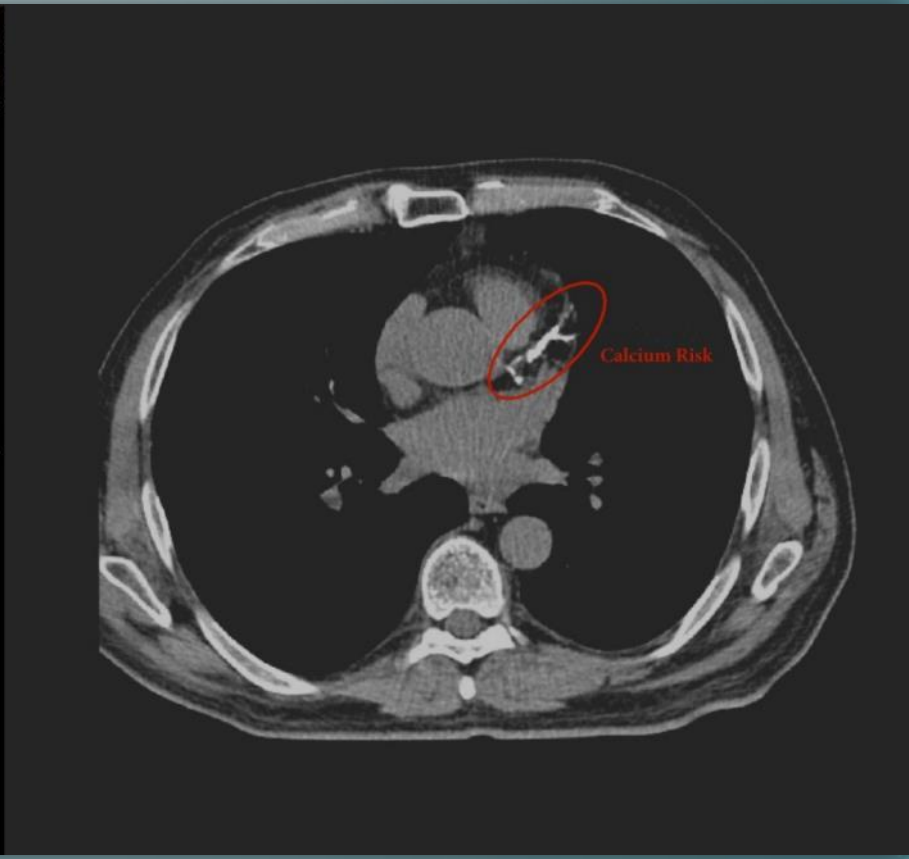
The CT Scan – and the CAC Score





The CT Scan – and the CAC Score





Framingham Versus Calcium Scoring & CAC

Muddy Waters: *Framingham Risk Score*	***AND WITH YOUR CAC SCORE ?***				
	0	1-80	81-400	401-600	>600
10%	?	?	?	?	?

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10%	**2.4%**	**5.4%**	?	?	?

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Muddy Waters: *Framingham Risk Score*	***AND WITH YOUR CAC SCORE ?***				
	0	1-80	81-400	401-600	>600
10%	**2.4%**	**5.4%**	**16%**	?	?

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	0	1-80	81-400	401-600	>600
10%	2.4%	5.4%	16%	25%	36%

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MUDDY FRAMINGHAM TAKES A GUESS...

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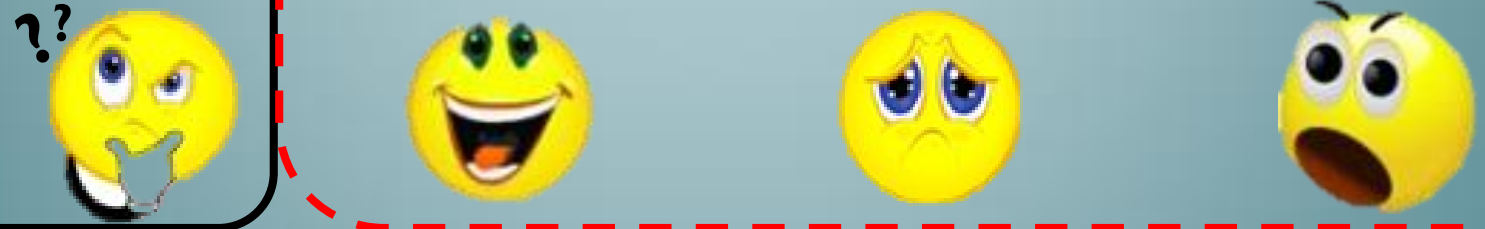

MUDDY FRAMINGHAM TAKES A GUESS...

THE CALCIUM SCAN **SEES** THE DISEASE.

Always the best test, across all the studies….

Study	Screening Power of CAC Scoring
2005 St Francis Heart	**Predicted ~10x Risk with CAC > 100 Vs CAC < 100** (*after RF adjustment, and CRP failed*)
2008 MESA	**Predicted ~8x Risk with CAC > 100 Vs CAC < 100** (*after RF adjustment*)
2003 Kondos et Al	**Predicted ~7x Risk with CAC > 170 Vs CAC < 170** (*after RF adjustment*)
2005 Taylor et al	**Predicted ~12x Risk with CAC > 0 Vs CAC < 0** (*after RF adjustment, and CRP failed*)
2005 Yeboah et al	**CAC beat all predictors as always** (CIMT, brachial flow dilation etc. failed again).
2008/2010/2012 Pencina/Polonsky et al	**CAC *re-classified* ~60% of Middle-Risk people…20% became High-Risk, 39% became Low-Risk** ***(CAC blew away CIMT and other predictors by a full order of magnitude)***
Budoff et al 2009	**CAC = 1 to 10 showed 20x more first-year events vs. CAC = 0 (note factor changes over time…!)**
Raggi/Greenland et al 2000/2010	**CAC > 400 had 4.8% cardiac events per year, versus 0.1% for CAC = 0.** Greenland et al verified CAC = 0 had **0.1% events over 3-5 years, independent of Risk Factors…**

Screening for Ischemic Heart Disease with Cardiac CT: Current Recommendations Volume 2012, Article ID 812046, http://dx.doi.org/10.6064/2012/812046

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Coronary Calcium is not a 'Risk Factor'

CALCIUM SEES THE DISEASE PROCESS ITSELF

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And what about CAC Score progression ??

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Yearly CAC Score Increase High (more than15%)

Starting Score 100-1000 → **3.5 Years Pass by…**

"Progression of Coronary Artery Calcium and Risk of First Myocardial Infarction in Patients Receiving Cholesterol-Lowering Therapy"
Paolo Raggi, Tracy Q. Callister, Leslee J. Shaw. Arterioscler Thromb Vasc Biol, 2004. DOI: 10.1161/01.ATV.0000127024.40516.ef

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Starting Score 100-1000 → **6 Years Pass by…**

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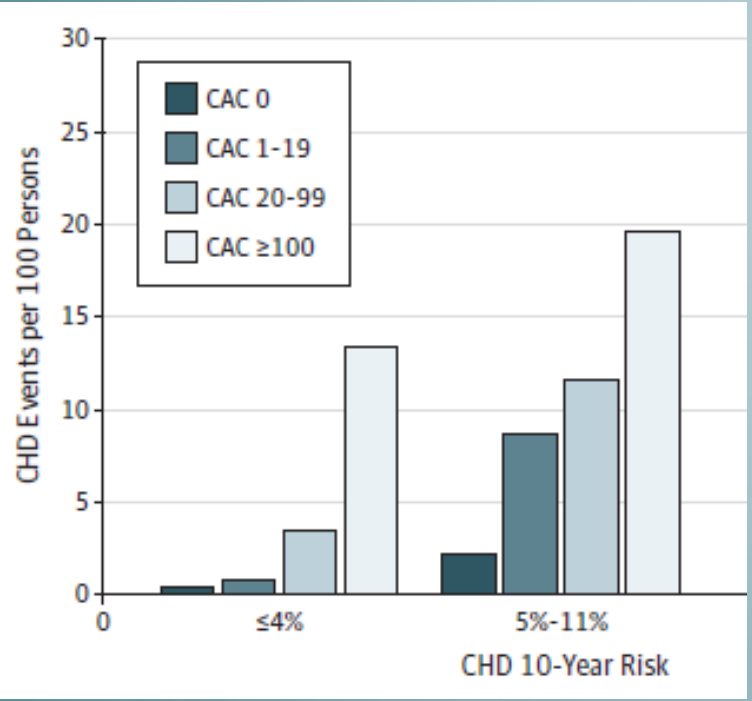
Very Latest Data…Feb 8th 2017 Study



- **Adults aged 32 to 46 followed**
- **Mean event follow-up 12.5 years**
- **CAC score makes a farce of "risk factors"…**
- **…because it ain't guessing.**

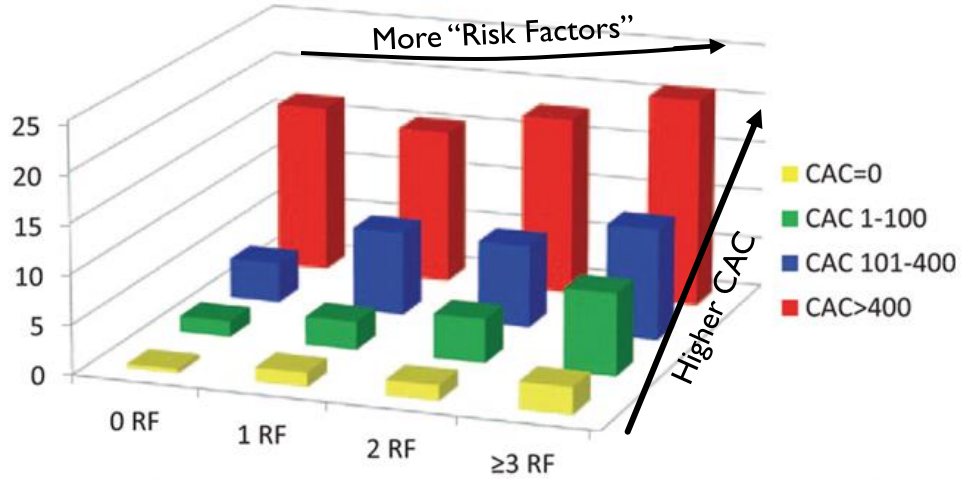
"Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death"

JAMA Cardiol. doi:10.1001/jamacardio.2016.5493
Published online February 8, 2017.

CAC Score is now obligatory for all US presidents and all Astronauts

BUT…If CAC Score Obliterates the "Risk Factors"…

Mortality rate (per 1000 person-years) with increasing coronary artery calcium (CAC) scores according to burden of risk factors (RFs).



	0 RF	1 RF	2 RF	≥3RF	Total
CAC=0	9,805	4,558	3,322	2,123	19,898
CAC					1
CAC					
CAC>					
Total	18,819	10,093	8,754	6,386	44,052

…which it does

Khurram Nasir et al. Circ Cardiovasc Imaging. 2012;5:467-473

Then WHY doesn't LDLc correlate with it?

- Why do autopsy studies of the correlation between the extent of coronary atherosclerosis and serum cholesterol yield null results? The answer that the blood samples, mostly from acci-

- Why did Hecht et al. [7] fail to find no correlation between LDL and the coronary calcium percentile (correlation coefficient 0.06 with a scatter plot showing no visible correlation) for 304

- Why do studies that looked for a correlation between TC or LDL and the progression of atherosclerosis find no statistically significant association [12,16–24]? All 10 studies involved EBT/CAC

- LDL and the calcium score with Spearman correlation coefficients near zero? Multivariate analysis gave an odds ratio of 1.005 for LDL [9].

- Why in a study of 177 asymptomatic patients of intermediate risk of CHD did Ramadan et al. [14] find a null result (OR = 1.022, $p = 0.361$) for the odds of positive coronary calcification outcome and LDL in a multivariate model? The group studied had a wide range of both LDL levels and calcium scores.

- Why did Kronmal et al. [12] find among approximately 2900 individuals that the relative risk of incident coronary artery calcium associated with LDL was only 1.03 per 10 mg/dL and barely reached statistical significance (lower CI 1.01) whereas both HDL and triglycerides exhibited much stronger associations?

- Why were Takamiya et al. [15] unable to find any association

asymptomatic individuals judged free of CHD (Spearman's coefficient = 0.07 and 0.08, respectively). Even the correlation coeffi-

- Why for adults with familial hypercholesterolemia, did Jensen et al. [11] find that age-adjusted coronary calcium scores were not associated with cholesterol levels as assessed by either scatter plots or correlation coefficients?

- Why did Arad et al. [10] in the St. Francis Heart Study find no correlation ($r = 0.03$, $p = 0.15$) between LDL levels and coronary calcium scores in 4903 asymptomatic individuals?

The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression.
Medical Hypotheses 73 (2009) 596–600

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DIABETIC PHYSIOLOGY is the most powerful predictor of CAC Score

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DIABETIC PHYSIOLOGY is the most powerful predictor of CAC Score

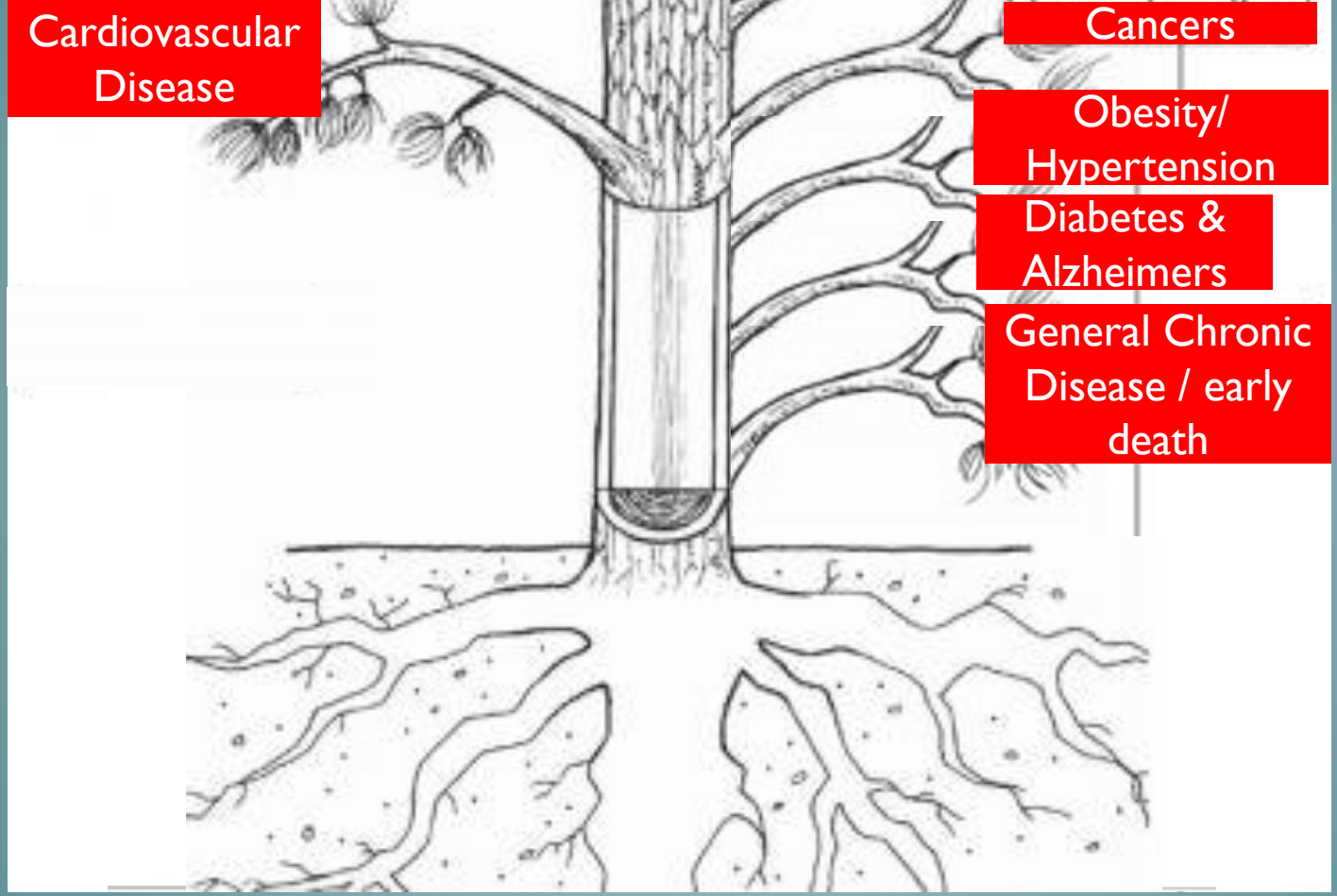
…LDL Cholesterol ***doesn't even show up***

The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression.
Medical Hypotheses 73 (2009) 596–600

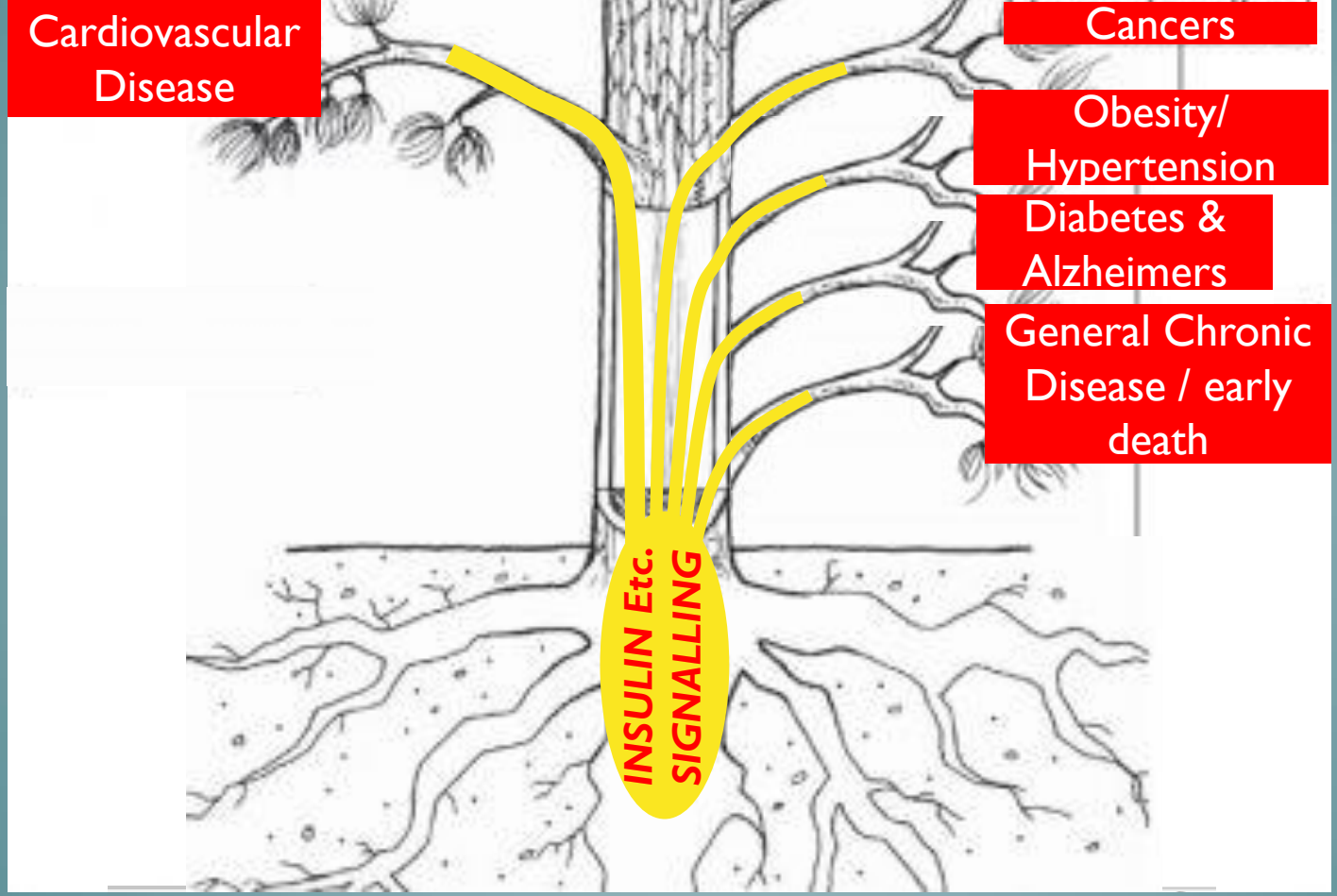
WRAPUP

"Striking at the Root"

What would I personally prioritise?



"There are a thousand hacking at the branches of evil - to one who is striking at the ***root*** *(causes)."*



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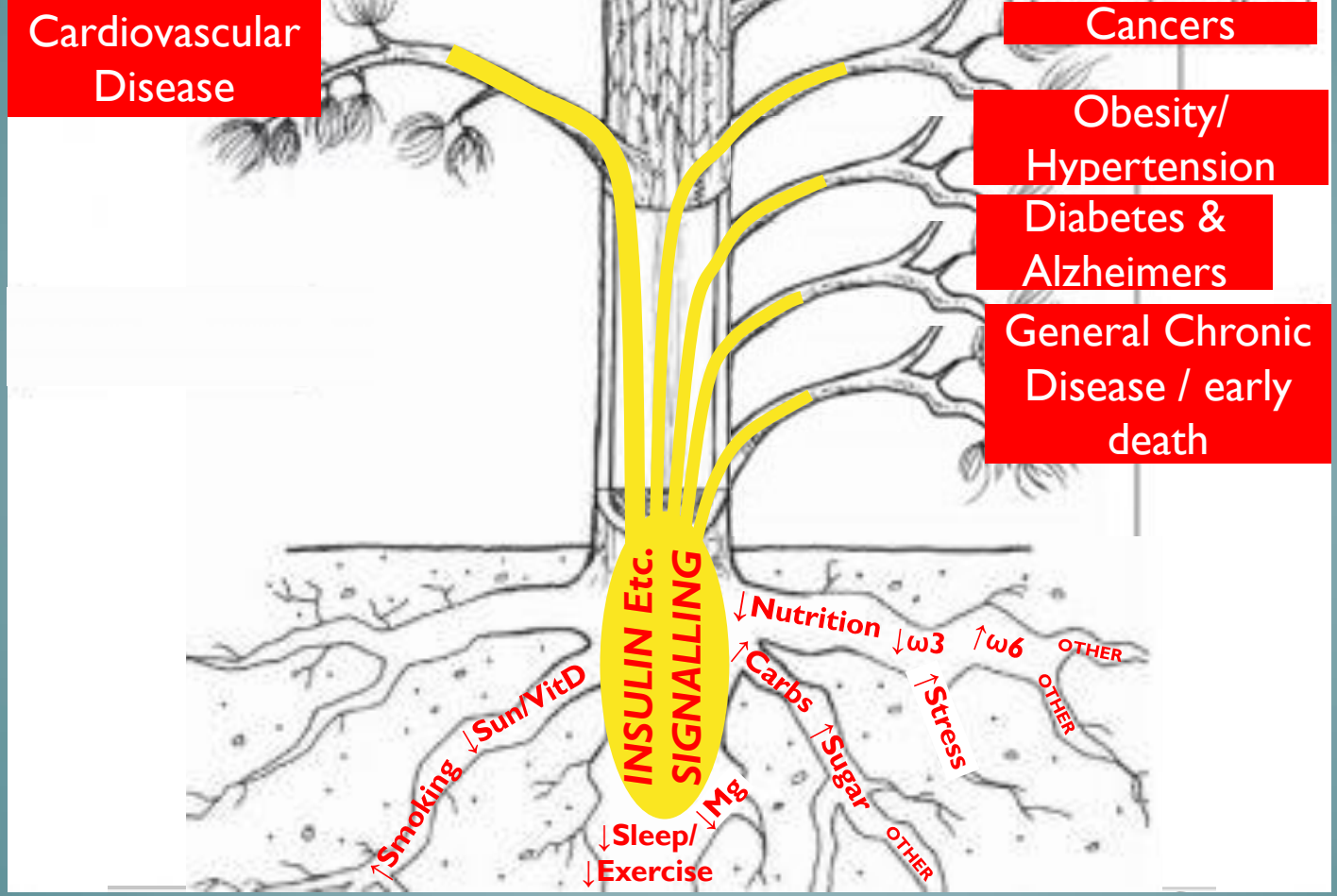

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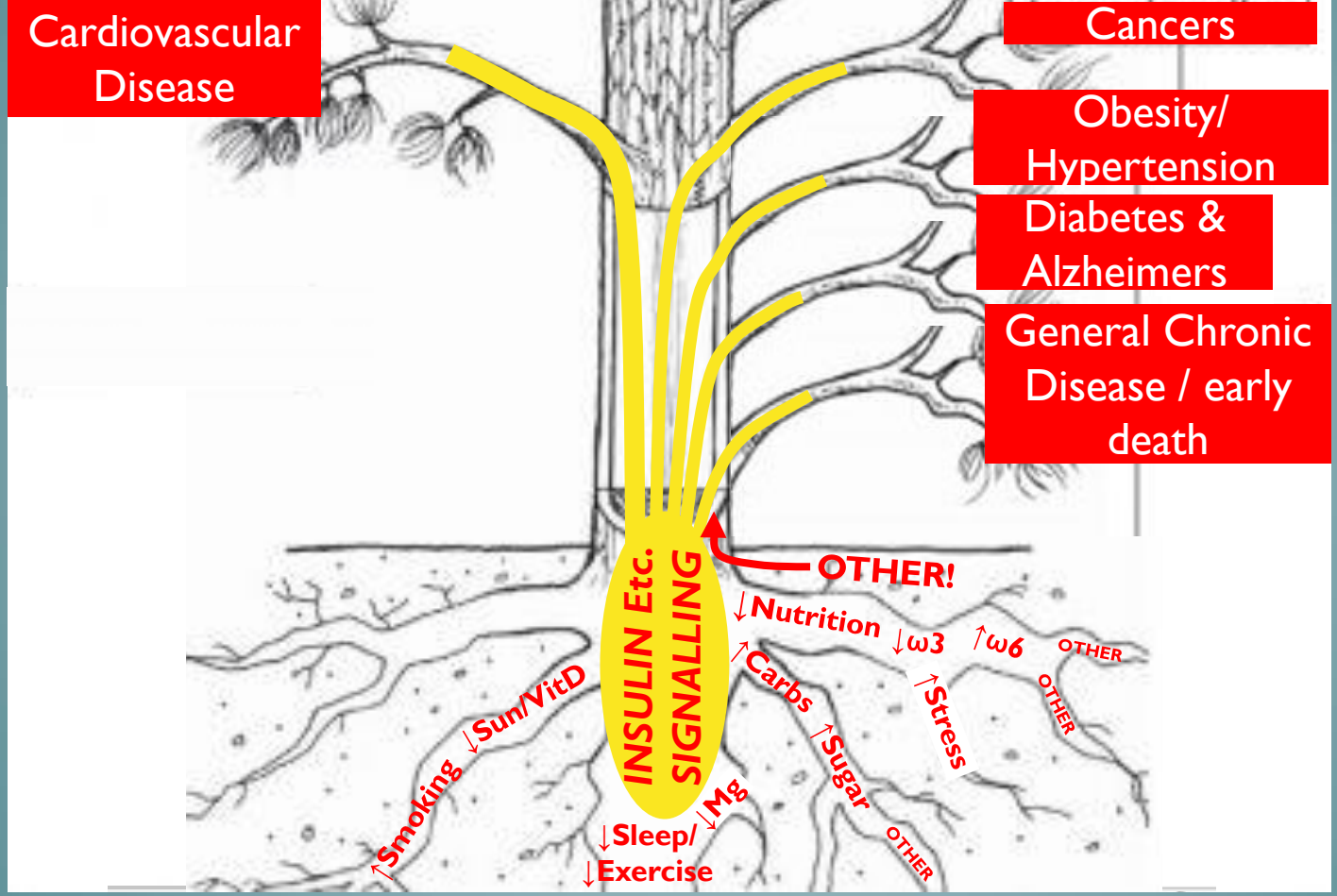

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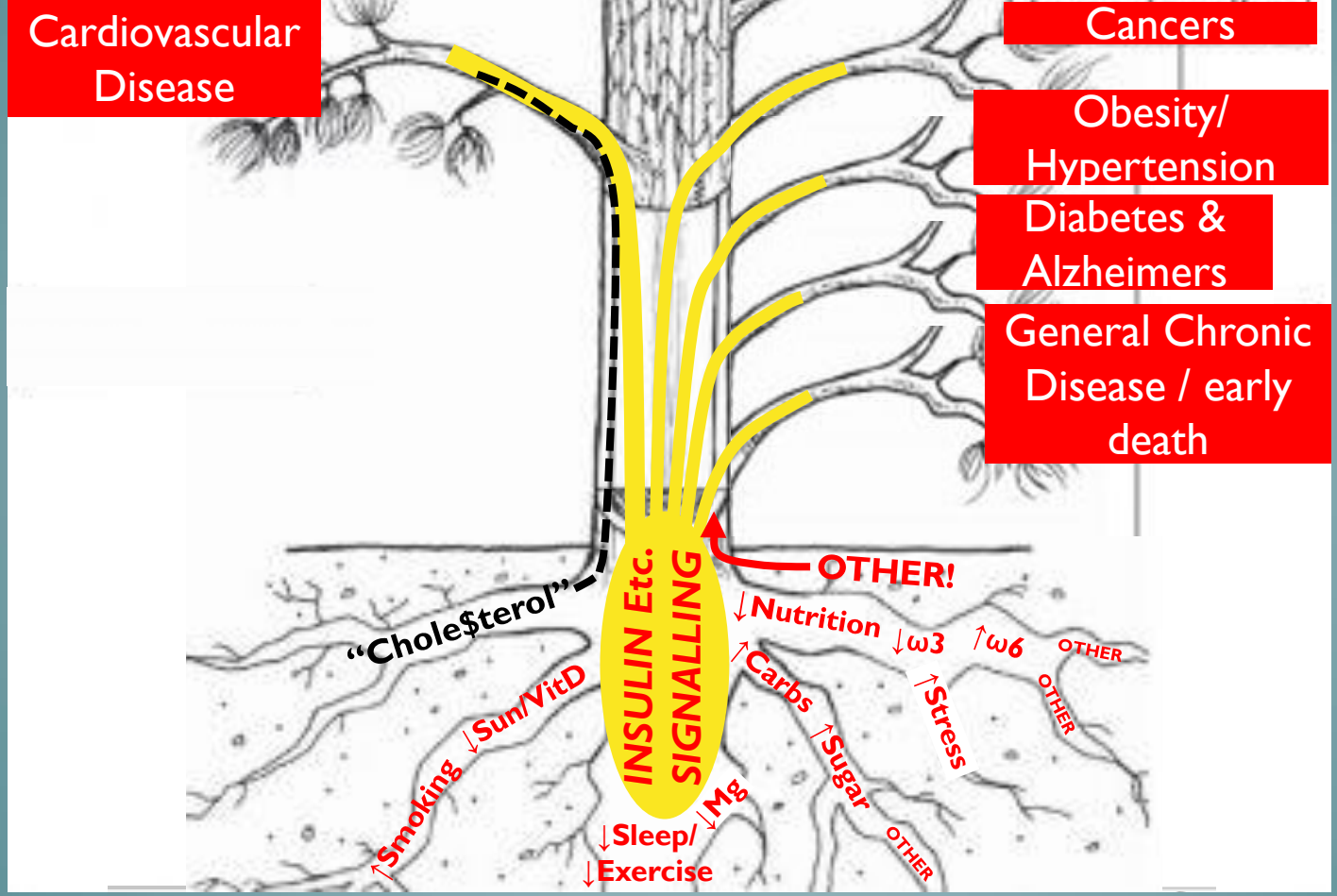

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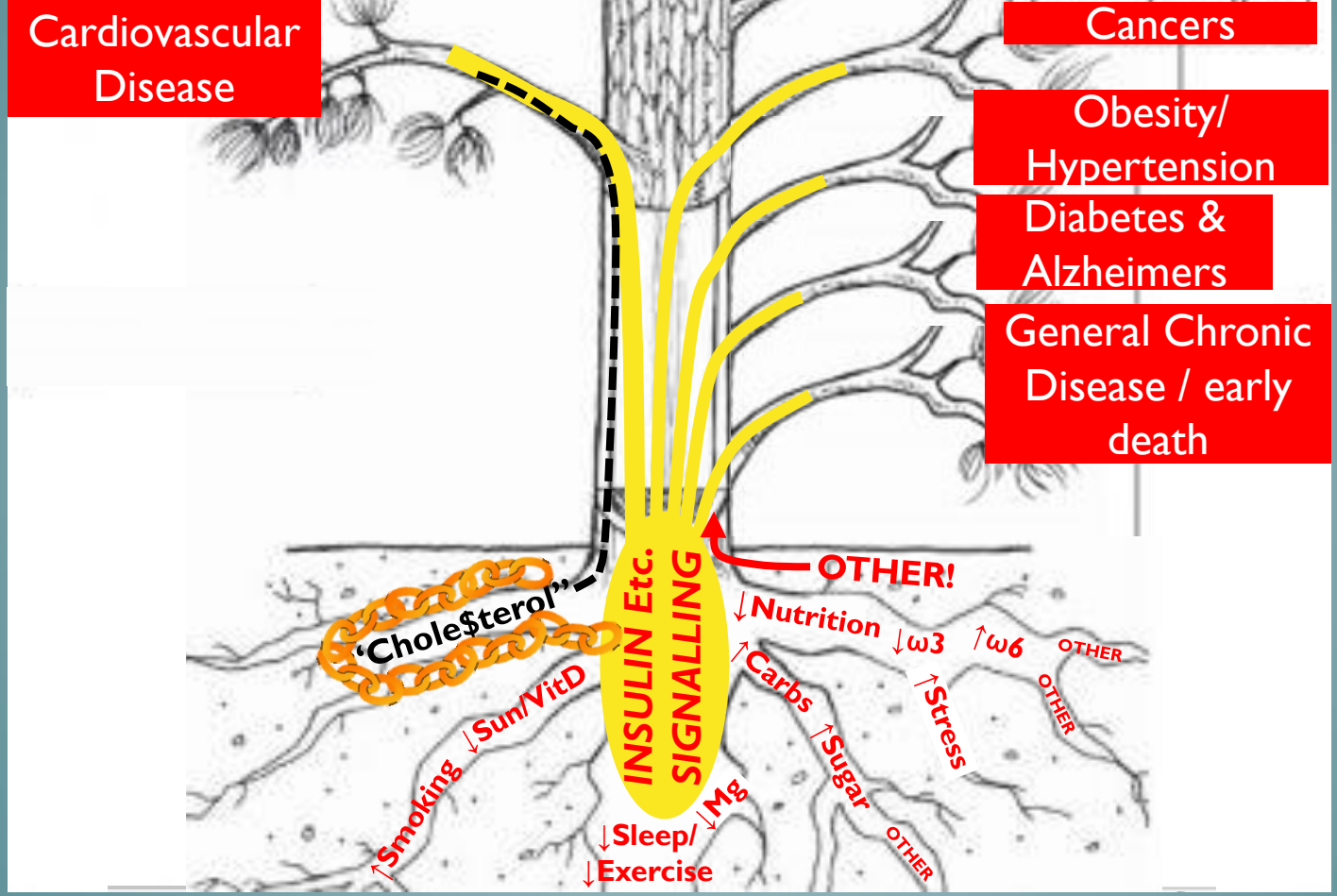

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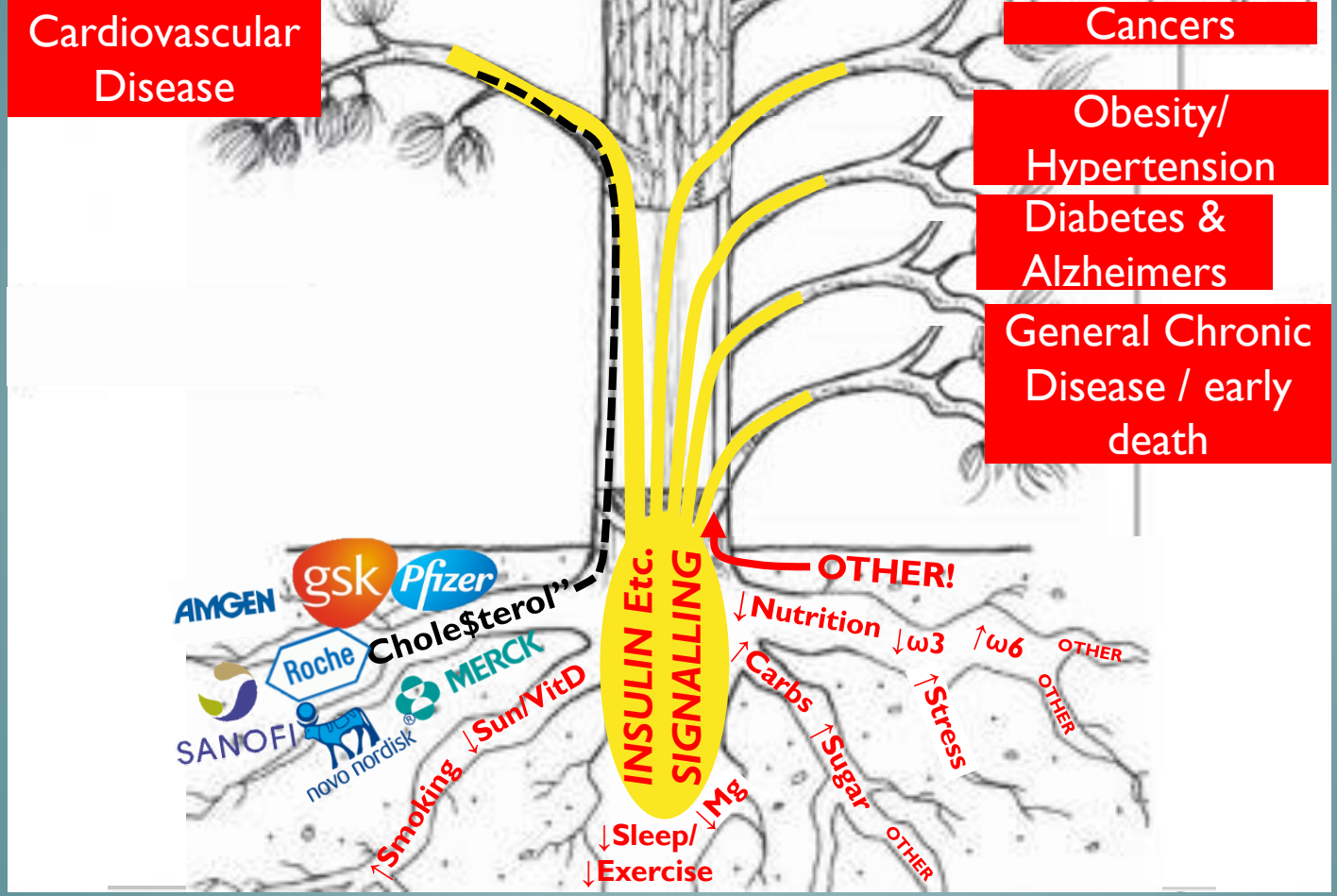

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