

DIABETES:
No Longer A Hopeless Disease

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Disclosures

Research Grant Support

NIH/NIDDK

Johnson & Johnson

Glaxo Smith Kline

HRSA x 3

Golden LEAF Foundation

Brody Foundation

***IF YOU WOULD LIKE TO ADD YOUR NAME TO THE LIST,
PLEASE SEE ME AFTER THE SESSION***

Board Membership

Surgical Review Corporation (Non-profit)













With a big farm ready for construction....

1978
East Carolina University



***“Let’s research
Together”***

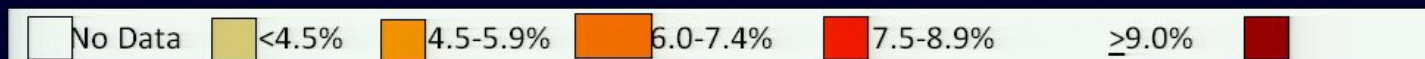
Obesity?

Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

Obesity (BMI ≥ 30 kg/m²)



Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at
<http://www.cdc.gov/diabetes/statistics>

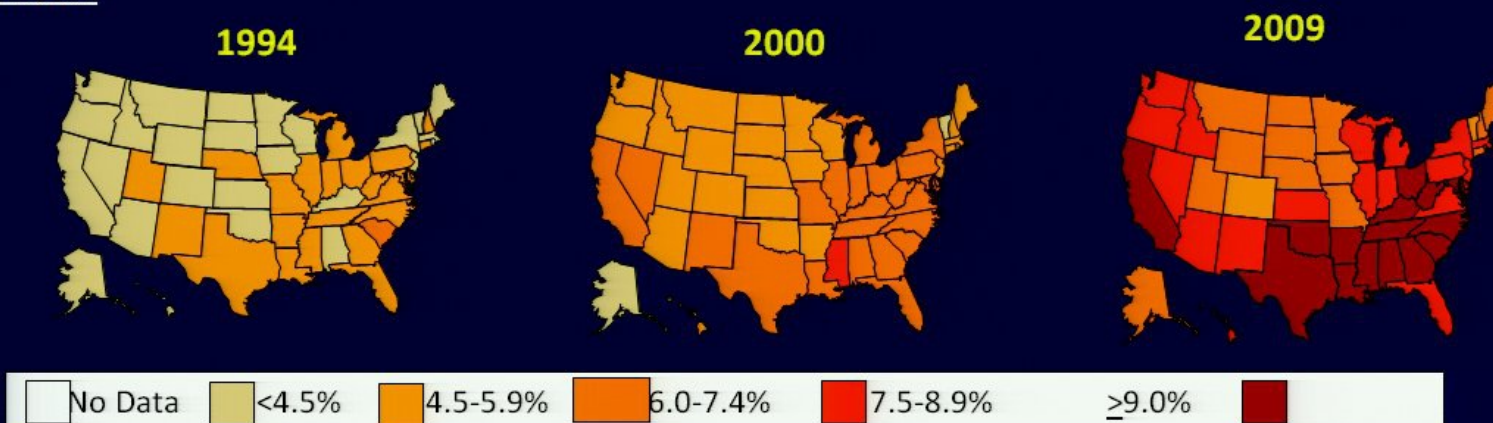


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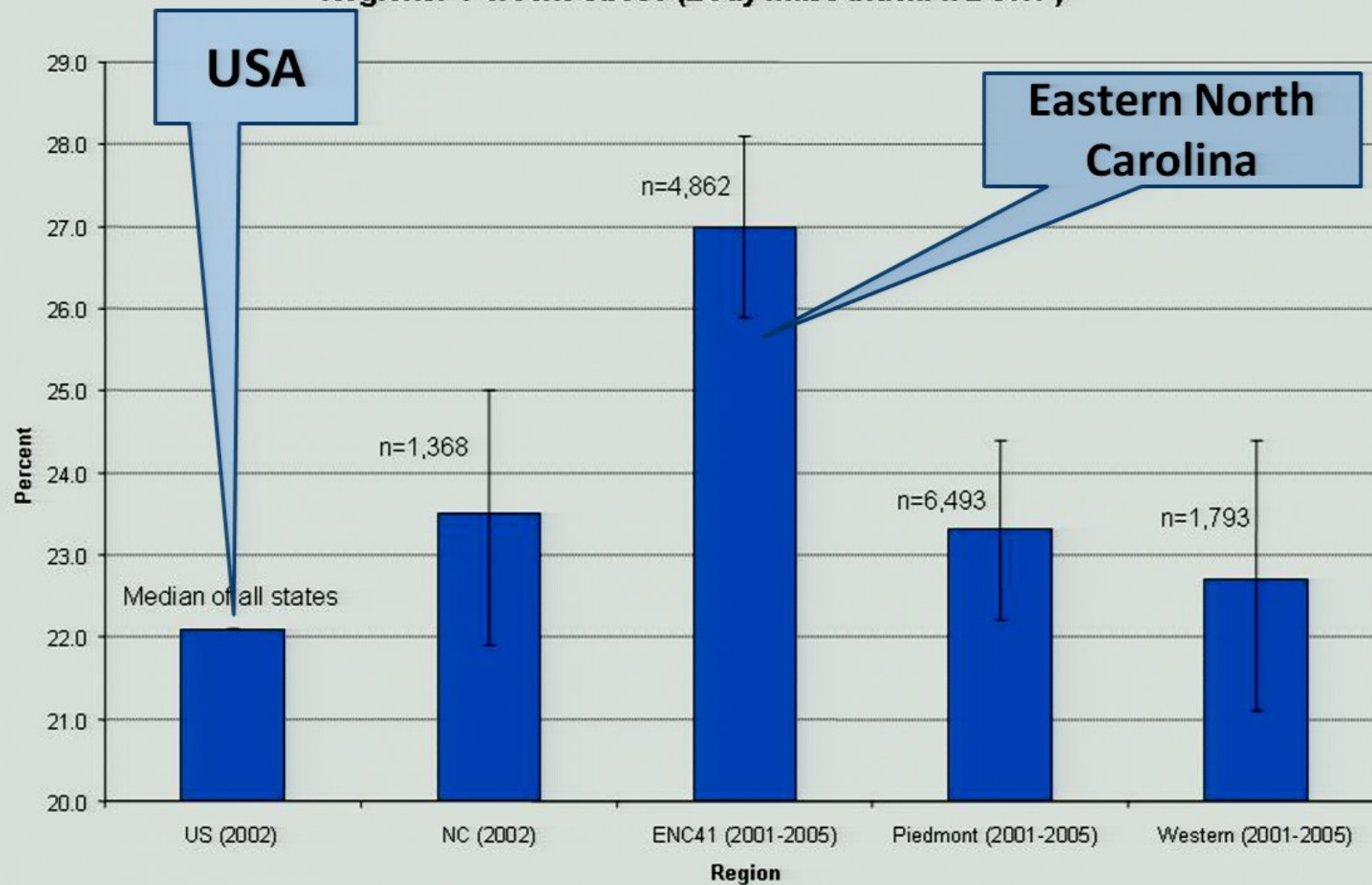
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- ***Obesity is the most prevalent, fatal, chronic disease of the 21st Century, increasing at a rate seen before only in infectious disease.***
- ***64.5 % of adult Americans are overweight or obese, even more in minorities***

Regions: Percent Obese (Body Mass Index: $x \geq 30.0$)



Data Source:
State: NC State Center for Health Statistics BRFSS Program
US: Centers for Disease Control

Center for Health Services Research and Development
East Carolina University
Greenville, NC

IT'S NOT JUST ABOUT WEIGHT!

The co-morbidities are even worse

Diabetes

Sleep apnea

Hyperlipidemias

Pulmonary Failure

Asthma

Hypertension

Infertility

Depression

Arthritis

Heart disease

Stroke

Hernias

Pseudotumor cerebri

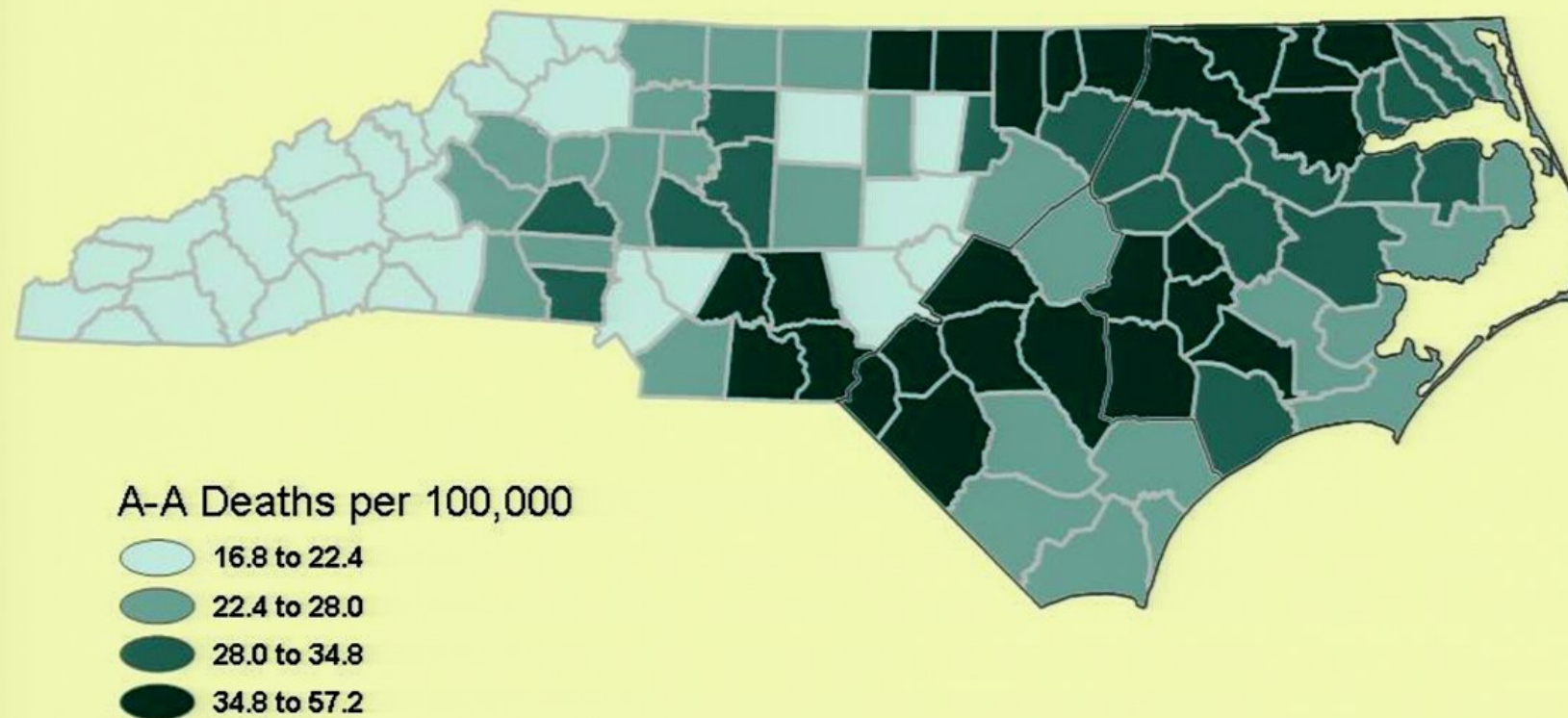
Immune suppression

Reflux

Stress incontinence

Pulmonary embolism

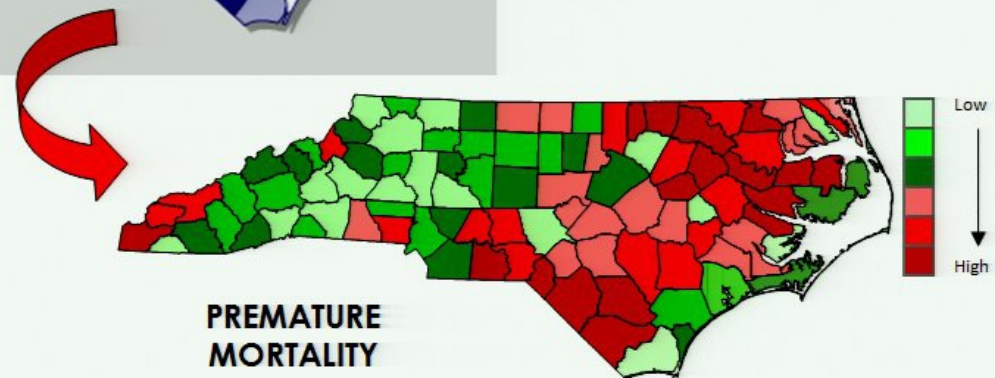
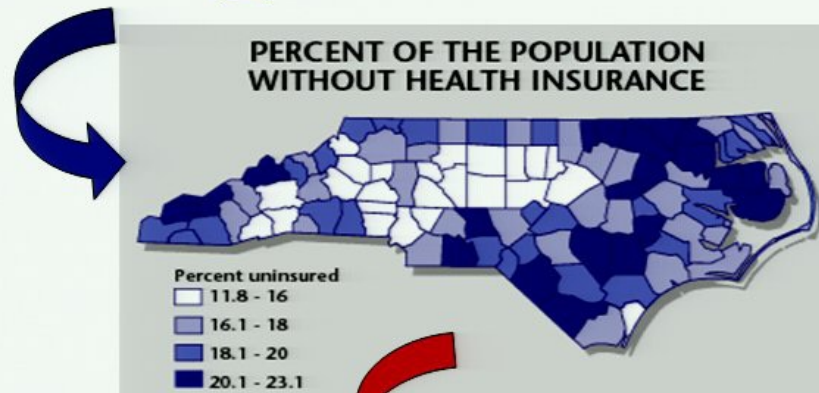
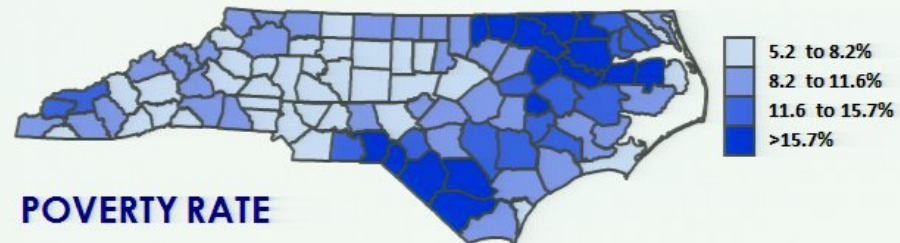
North Carolina 2001 to 2005: Total Population Age-Adjusted Mortality Due to Diabetes Mellitus



Data Source: Odum Institute—UNC, Chapel Hill (NC-SCHS)
Age-adjustment based on the year 2000 US Standard Million Population

Center for Health Services Research and Development
East Carolina University
Greenville, NC

Regional Convergence of Social Issues



Data for 1999

Center for Health Services Research and Development
East Carolina University

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- ***Pories: Chair of Surgery: ??????????????????***

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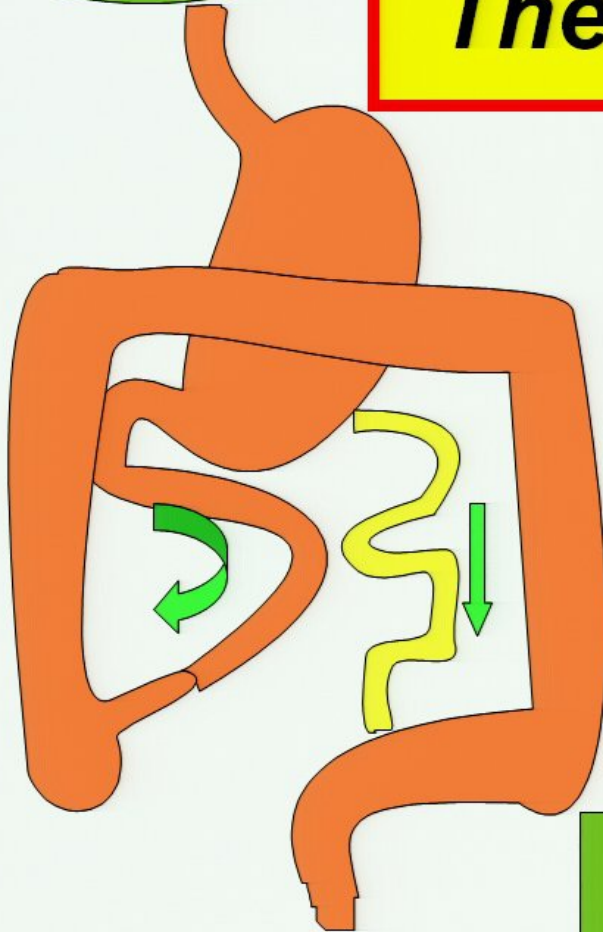
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NIH (1991) “Diets, Exercise, Drugs, behavioral modification are not effective in the severely obese”

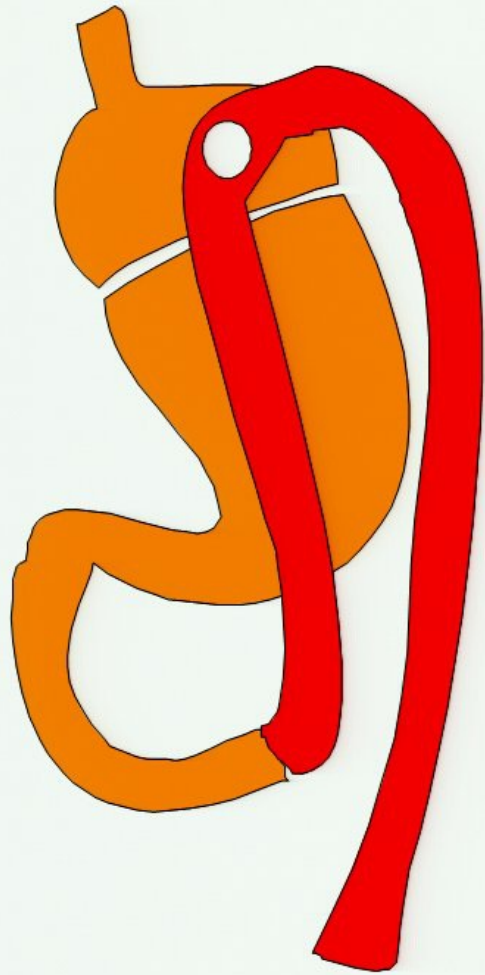
1950's

The intestinal bypass



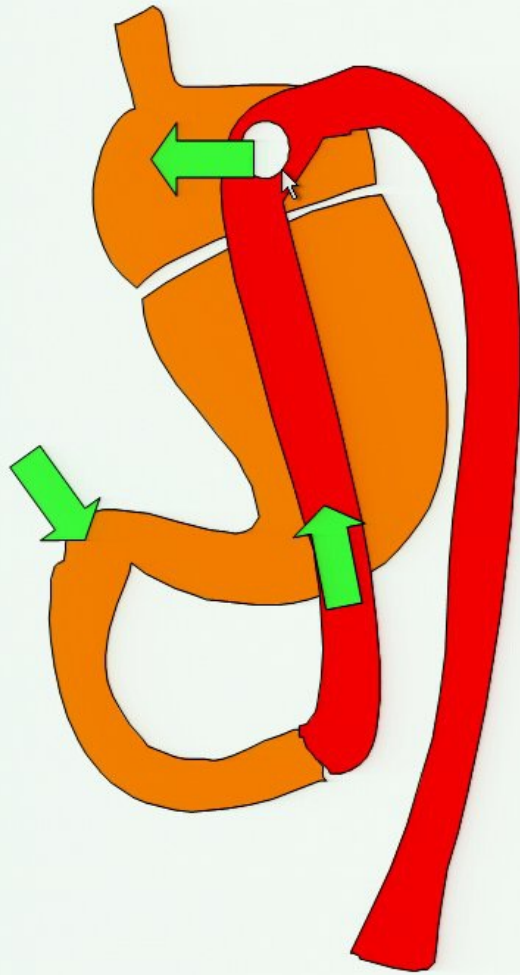
12 motions/day
Hypo-proteinemia
Liver failure
Kidney stones
Mineral loss
Many deaths

Not a great answer

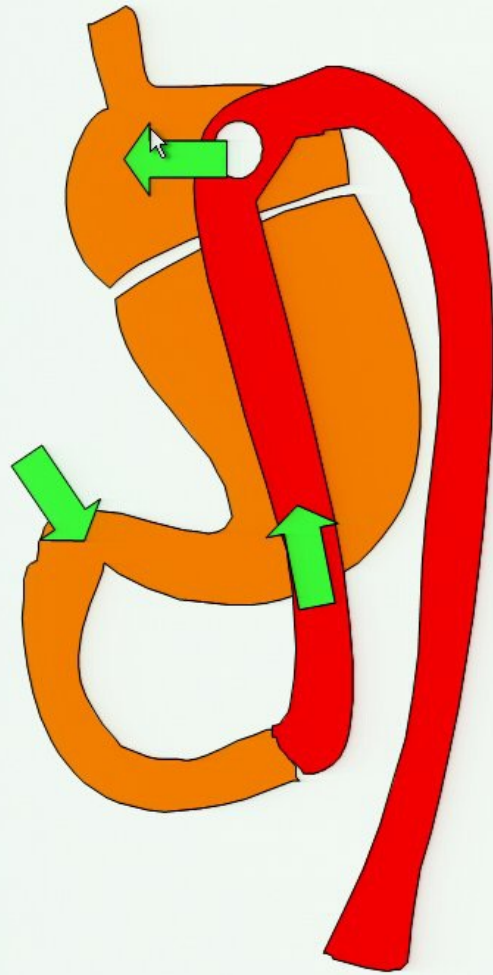


1960's

Mason Gastric Bypass

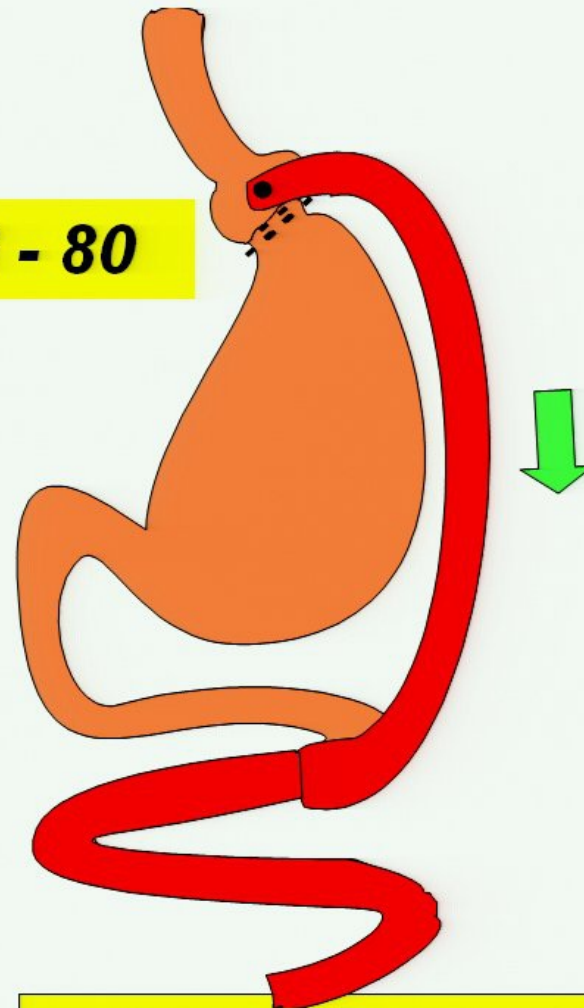


Mason Gastric Bypass



Mason Gastric Bypass

1978 - 80



Greenville Gastric Bypass

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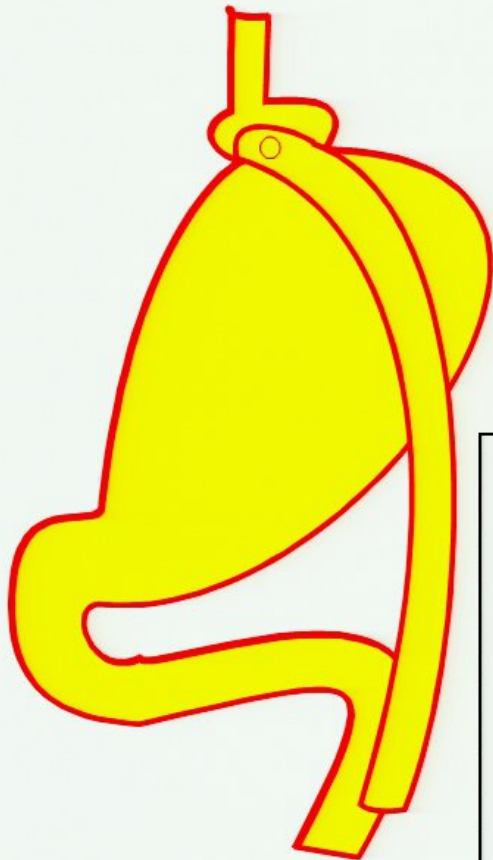
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- ***The unexpected answer is a gift***
- ***If the results cannot be reproduced by others, the conclusions are probably not true***

The Greenville Gastric Bypass



**30 ml gastric pouch
10 mm. anastomosis
60 cm alimentary loop**

Total group 1980-1998 = 831

16 year cohort = 147

95% Follow-up

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- *Illegal: HIPAA violation of patient privacy*

Weight Loss After Bariatric Surgery @ 16 Years (95% Followup)

	Mean Weight	Mean % XS Weight Loss	Mean BMI
Preop	317	0	51
1 year	199	67	32
2 years	194	69	32
5 years	209	57	34
10 years	217	51	35
16 years	211	55	37



106 lb

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2003 Schauer U Pitt-104 lb

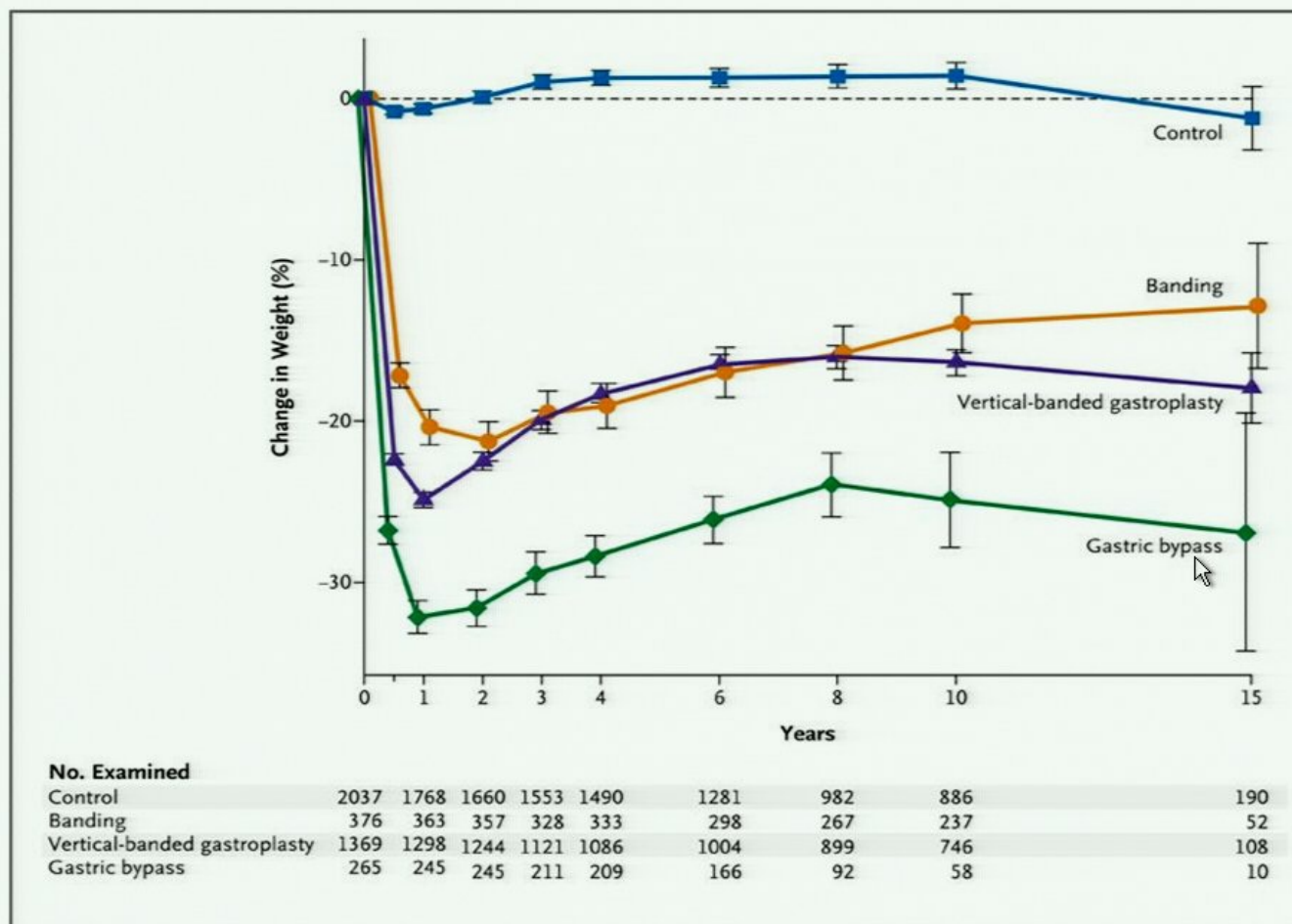


A morbidly obese woman who could not conceive...





Mean % Weight Change over 15 Years Swedish Obesity Study



Sjostrom: NEJM 2007;357:741-52



Conclusion #1: Severe obesity is no longer a hopeless disease. The gastric bypass produces durable, significant weight loss.



The next challenge:

“Walter, I have a patient who needs a gastric bypass but she has diabetes.....”

Type 2 Diabetes

- ***Progressive, irreversible disease***

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- ***OK, we'll accept the patient but be aware that in these severely obese high-risk patients, control of the diabetes may be a problem***

And the mystery:

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- ***Second patient: plasma glucose normal***
- ***Third patient: plasma glucose normal***
- ***“Do you guys know how to diagnose diabetes?”***
- ***Fourth patient: plasma glucose normal***
- ***“It’s the lab’s fault!”***

Remission of diabetes after gastric bypass

Pt. LT

***Insulin
Requirements
Pre & post
Gastric
Bypass***

Date	Glucose	Insulin given
16 Nov '80 PREOP/OP	495	90
17 Nov	281	8
18 Nov	308	16
19 Nov	240	8
20 Nov	210	4
21 Nov	230	8
22 Nov	216	4
28 Nov	193	0
30 Nov	153	0
14 Dec	155	0

608 morbidly obese: Mean 9 yrs

**165 Type 2
Diabetics**

**165 IGT
“impaired”**

**146 long enough
followup**

**152 long enough
followup**

**121/146 (83%)
euglycemic**

**150/152 (99%)
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Does the glucose level really matter?

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**Schauer:
1,160 pts.; mean 5 yrs
83% remission**

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Does the glucose level really matter?

- ***The gastric bypass operation produces rapid, full and durable remission of type 2 diabetes mellitus!***
- ***Are you sure you're just not reducing glucose values?***
- ***Is there a difference in health outcomes?***

232 Morbidly Obese Diabetics

154

Gastric Bypass

14/154 (9%)/ 9 yrs

1%/yr

78

**Operation refused
for personal or
insurance reasons**

22/78 (28%)/6.2 yrs

4.5%/yr

$P < 0.0003$

232 Morbidly Obese Diabetics

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Gastric Bypass

Mortality ↓ 78%

14/154 (9%)/ 9 yrs

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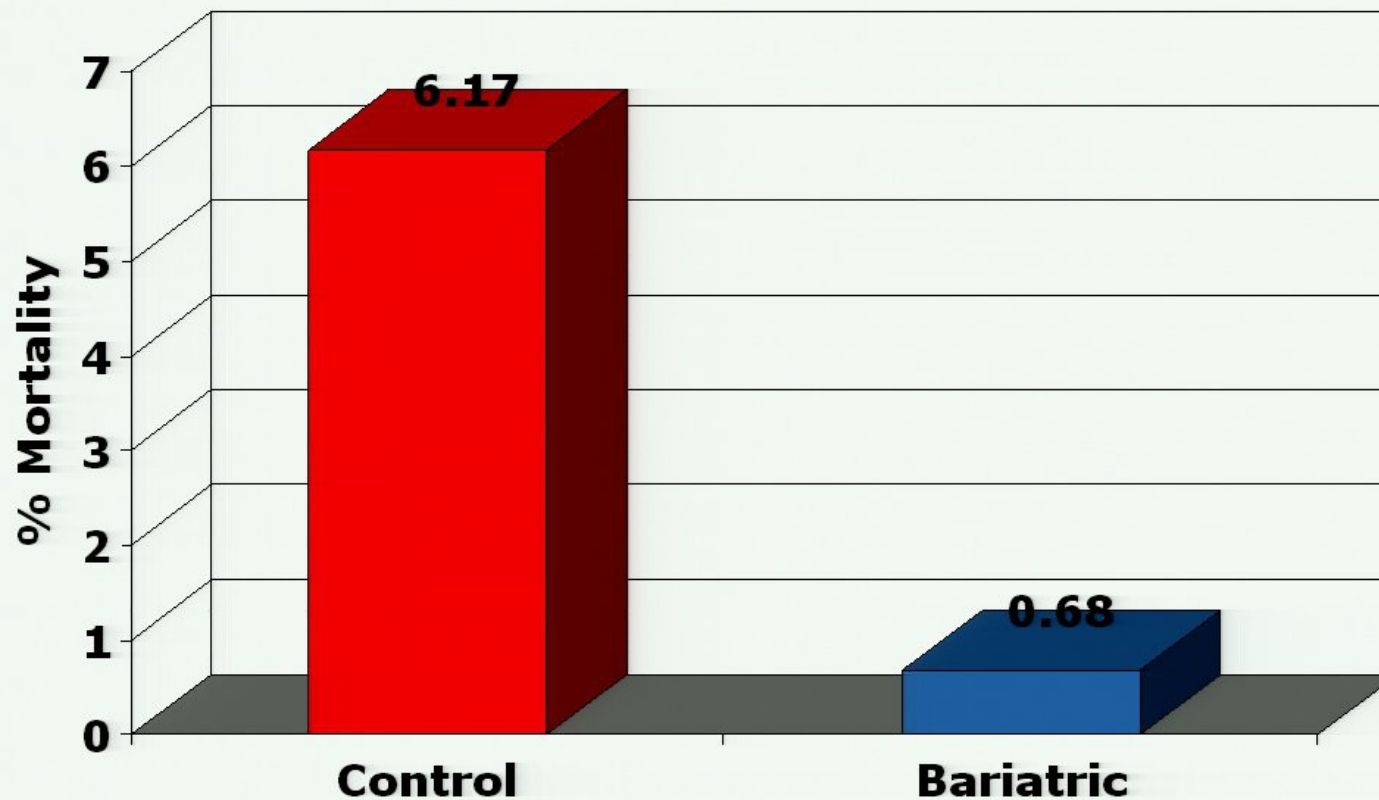
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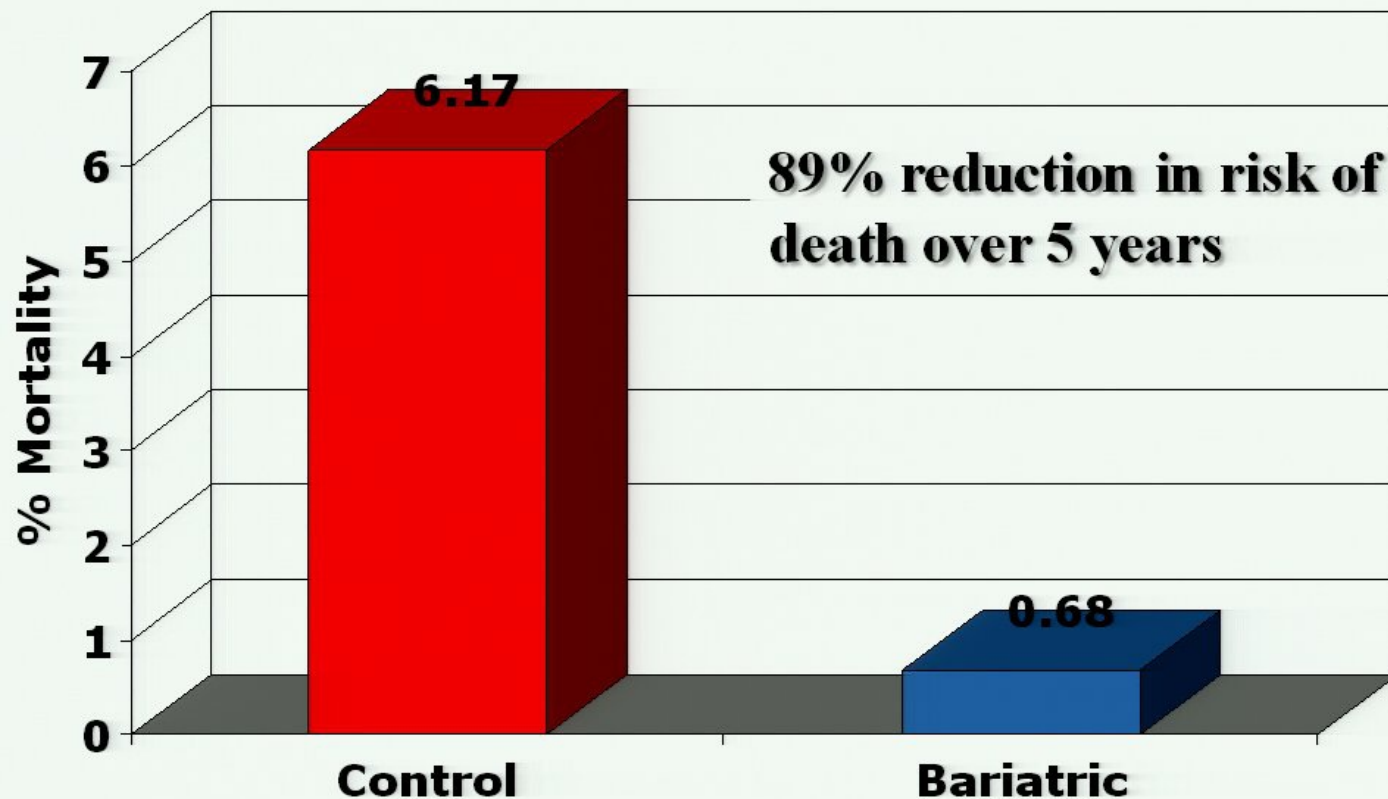
LONG-TERM SURVIVAL CANADA

Christou et al. Ann Surg 2004;240:416-424

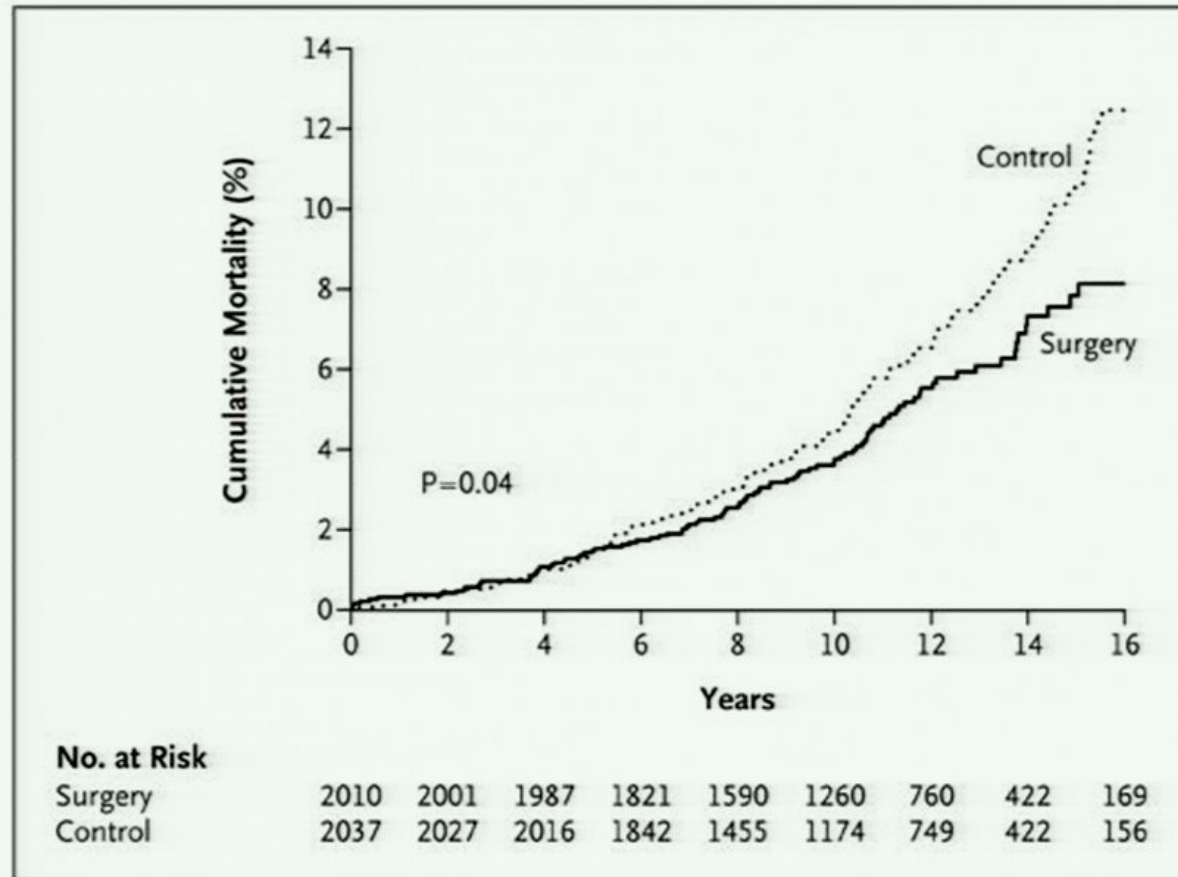


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Unadjusted Cumulative Mortality Swedish Obesity Study



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Conclusion # 2: The gastric bypass produces full remission of Type 2 Diabetes (T2DM) with a reduction in morbidity and mortality

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T2DM is no longer a hopeless disease!

ORIGINAL ARTICLE

Bariatric Surgery vs. Conventional Medical Therapy for Type 2 Diabetes

Geltrude Mingrone, M.D., Simona Panunzi, Ph.D., Andrea De Gaetano, M.D., Ph.D.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Page 1 of 1

Studies: Surgery can put diabetes into remission

MARILYNN MARCHIONE AP Chief Medical Writer Published: March 26, 2012 1:18PM

CHICAGO (AP) -- New research gives clear proof that weight-loss surgery can reverse and possibly cure diabetes, and doctors say it should be offered sooner to more people with the disease -- not just as a last resort.

The two studies, released on Monday, are the first to compare stomach-reducing operations to medicines alone for "diabesity" -- Type 2 diabetes brought on by obesity. Millions of Americans have this and can't make enough insulin or use what they do make to process sugar from food.

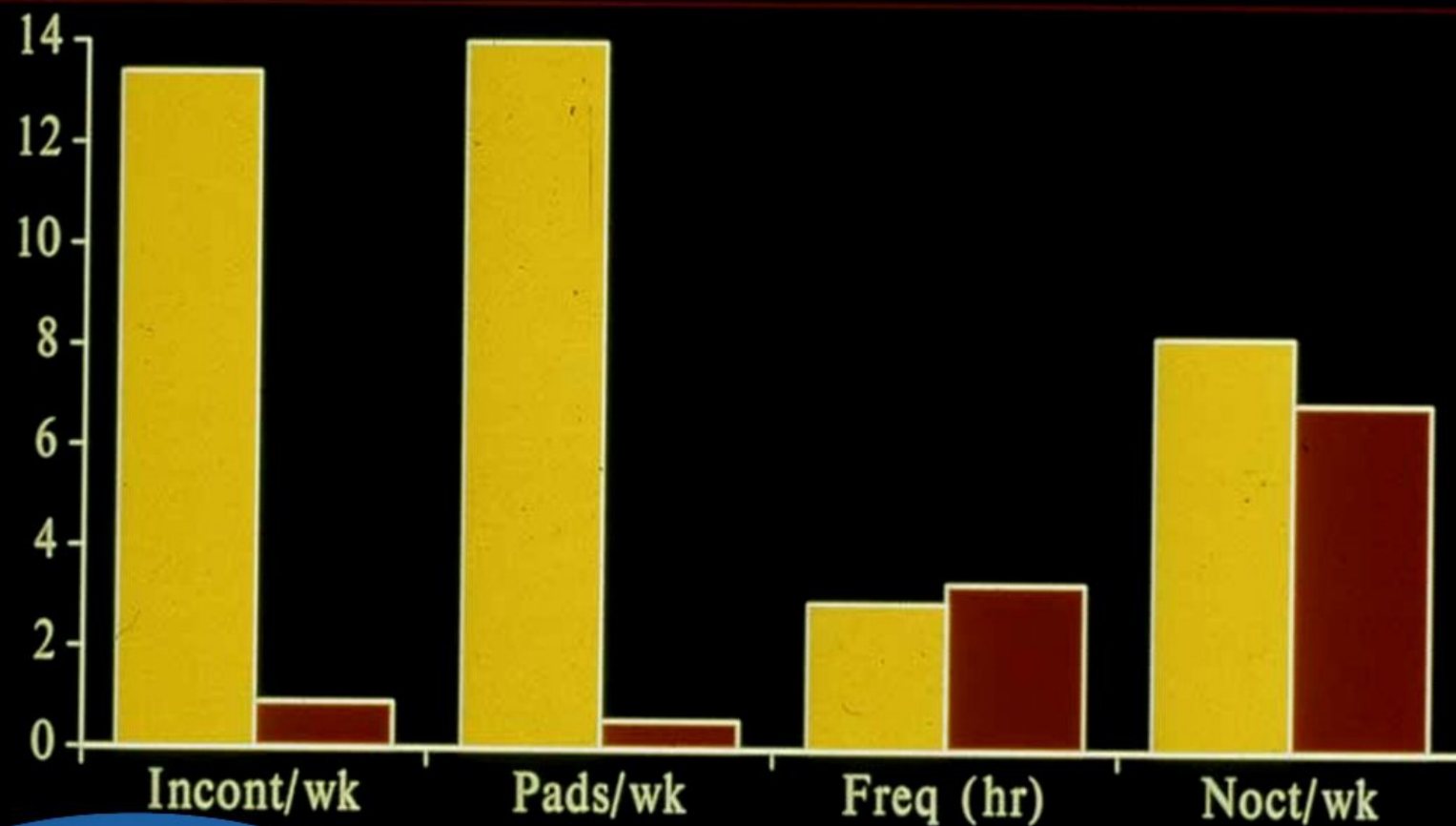
Both studies found that surgery helped far more patients achieve normal blood sugar than medicines alone did.



In this March 23, 2012 photo, Dr. Francesco Rubino, a surgeon at Weill Cornell Medical Center, joins his patient Tamikka McCray, 39, for an interview in New York. McCray no longer needed to take diabetes medication and insulin after her weigh-loss surgery. Research by Dr. Francesco Rubino, McCray's surgeon at Weill Cornell, and other doctors gives clear proof that weight-loss surgery can reverse and possibly cure diabetes. (AP Photo/Bebeto Matthews)

***But wait....
Something else is going on....***

Surgically Induced Weight Loss Effects on Urinary Diary Parameters



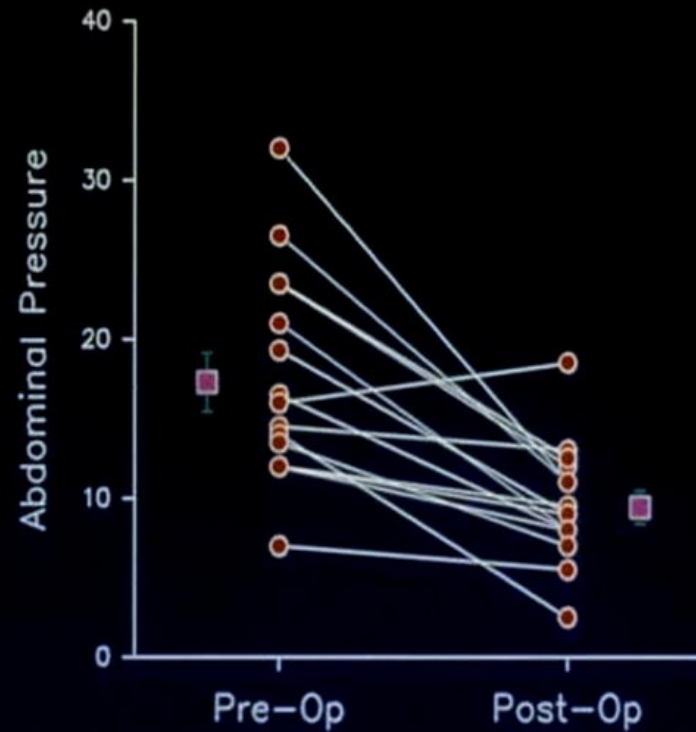
Sugerman et al.

Before Surgery

After Surgery

Morbid Obesity

Operative Changes in Abdo Pressure



Sugerman et al.

$p < 0.0001$



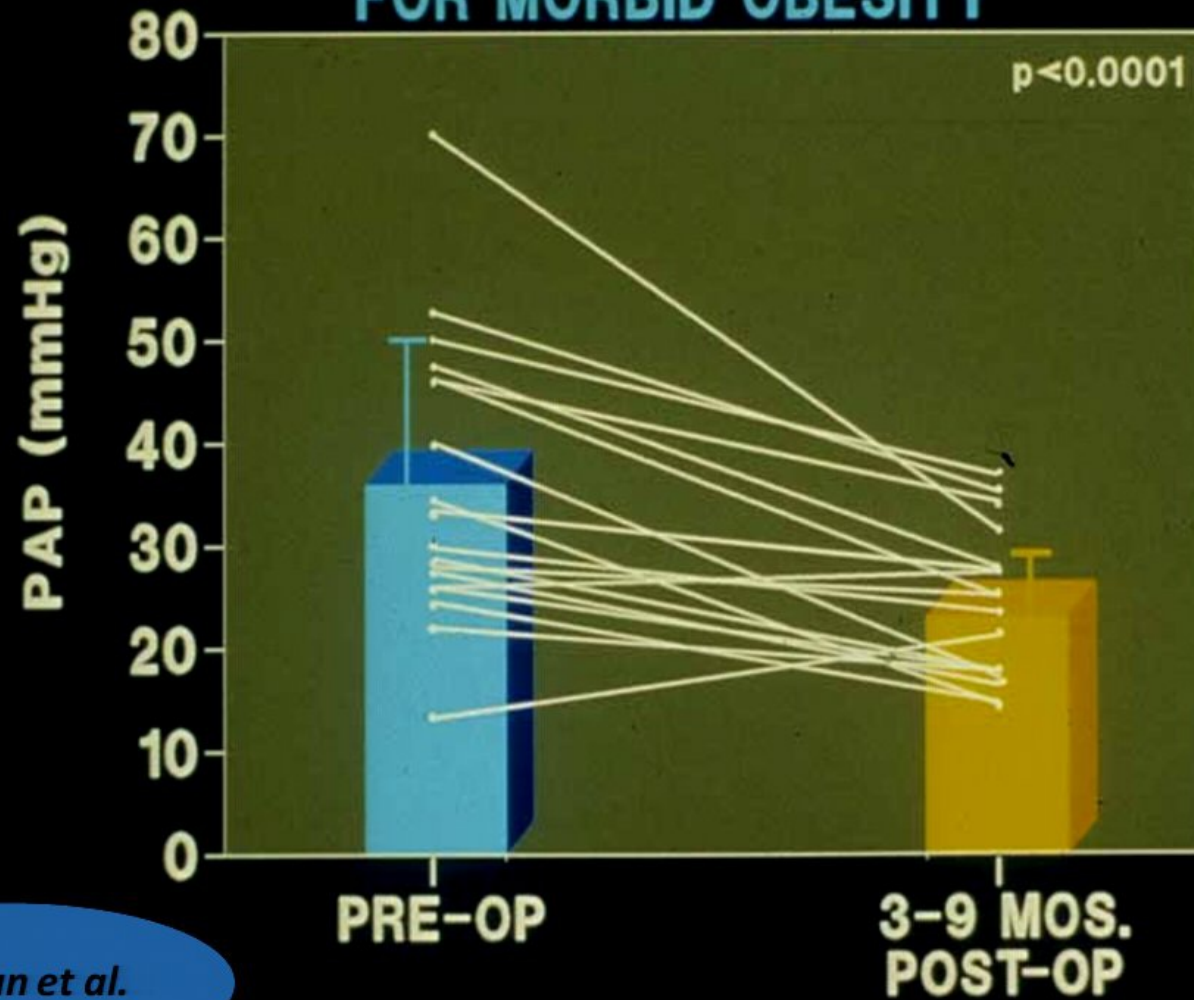
Sugerman et al.





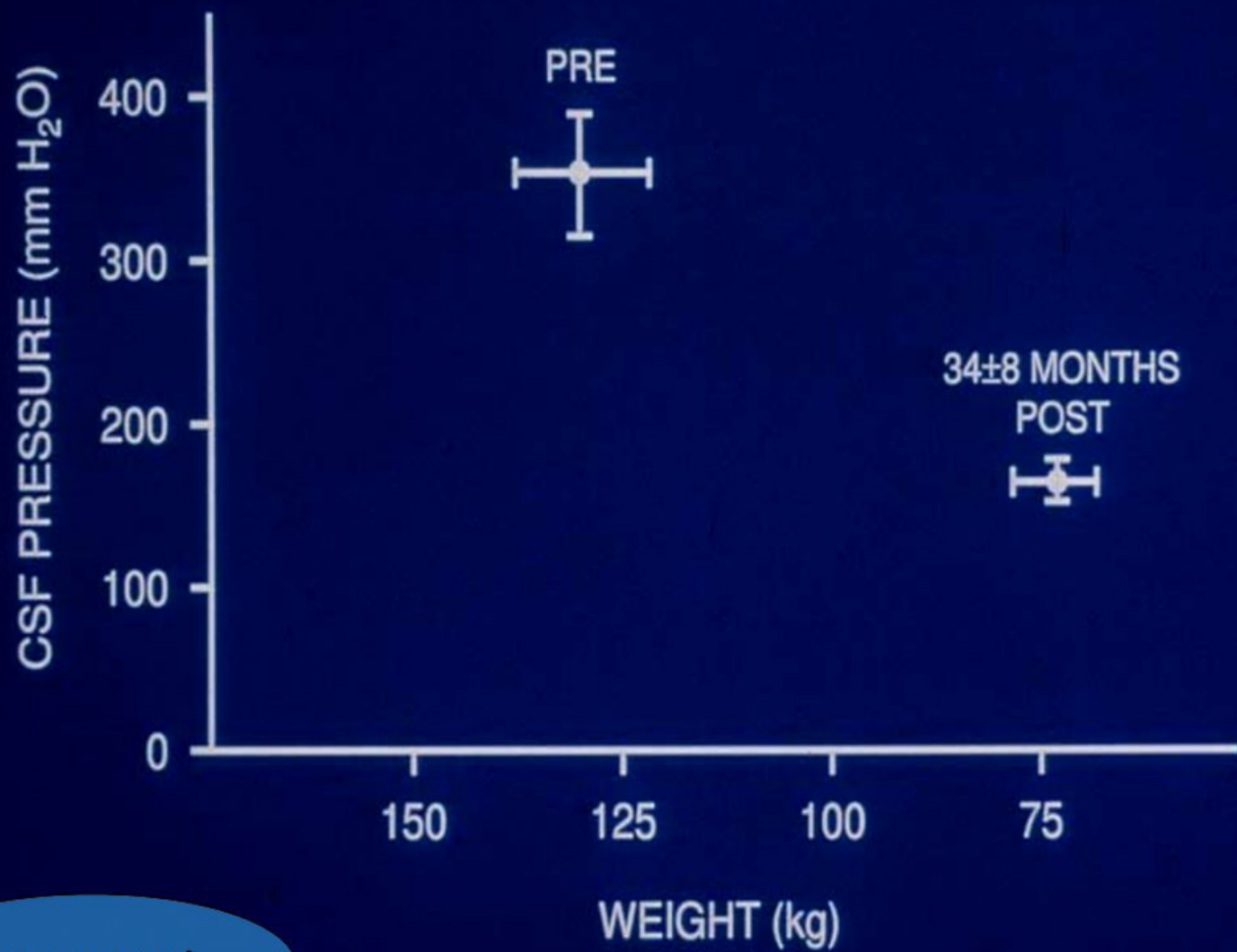
Sugerman et al.

PULMONARY ARTERY PRESSURE BEFORE AND AFTER SURGICALLY INDUCED WEIGHT LOSS FOR MORBID OBESITY



Sugerman et al.



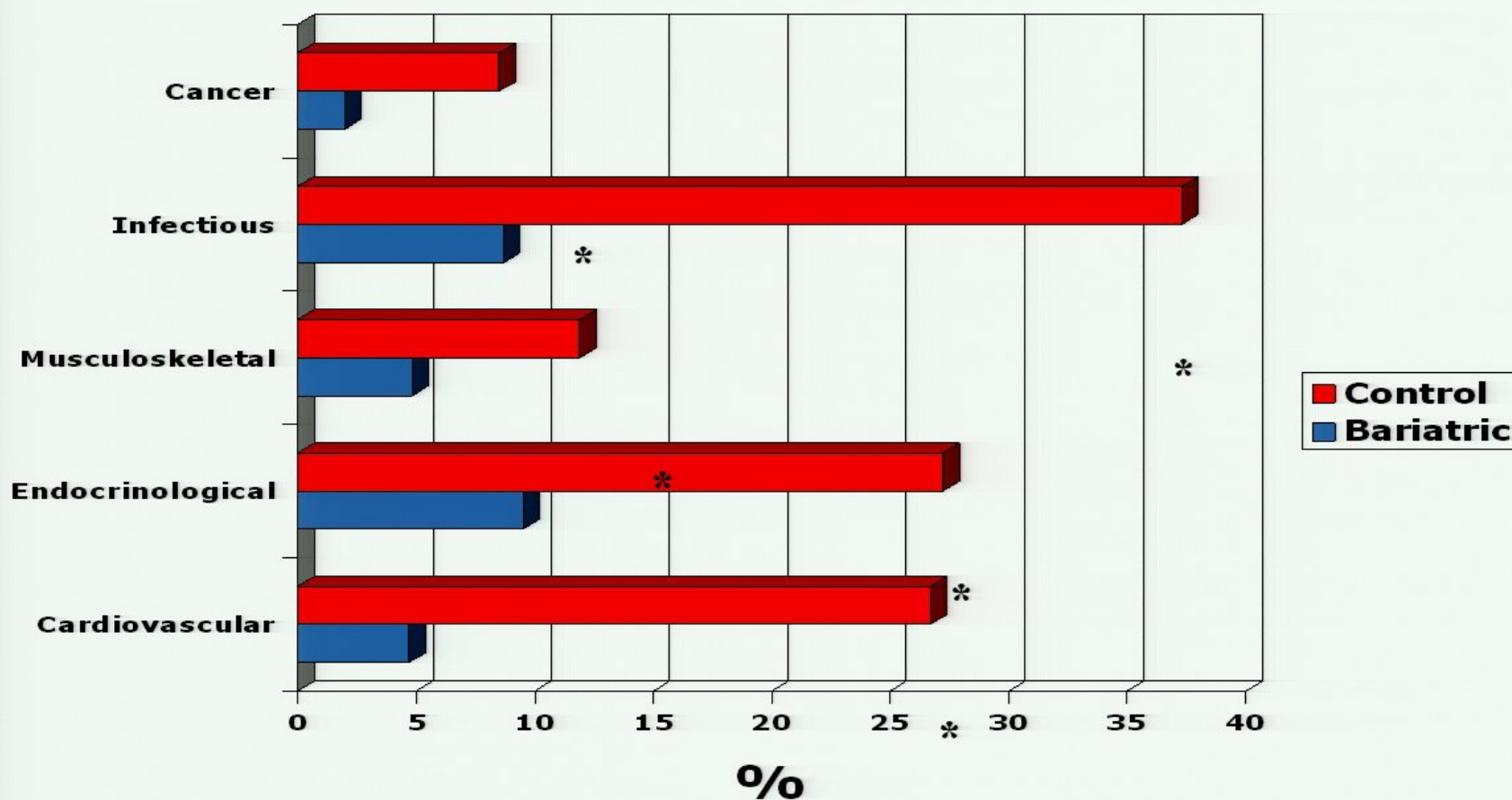


Sugerman et al.

Dr. Blackstone : Scottsdale Bariatric Center
% Resolution of Co-morbid disease

Co-Morbid Disease	Gastric Bypass	Revision	Adjustable Gastric Band
Type 2 Diabetes	80.5%	66.7%	78.6%
Hypertension	63.3%	50.0%	35.1%
Obstructive Sleep Apnea	68.9%	80.0%	59.2%
GERD	87.6%	73.9%	54.5%
Venous Insufficiency	71.0%	78.9%	60.4%
Infertility			
Asthma	66.0%	83.3%	37.5%
Stress Incontinence	84.0%	75.0%	57.1%
Depression	31.4%	33.3%	27.2%
DJD	67.1%	50.0%	49.3%
Hyperlipidemia	61.4%	50.0%	25.0%

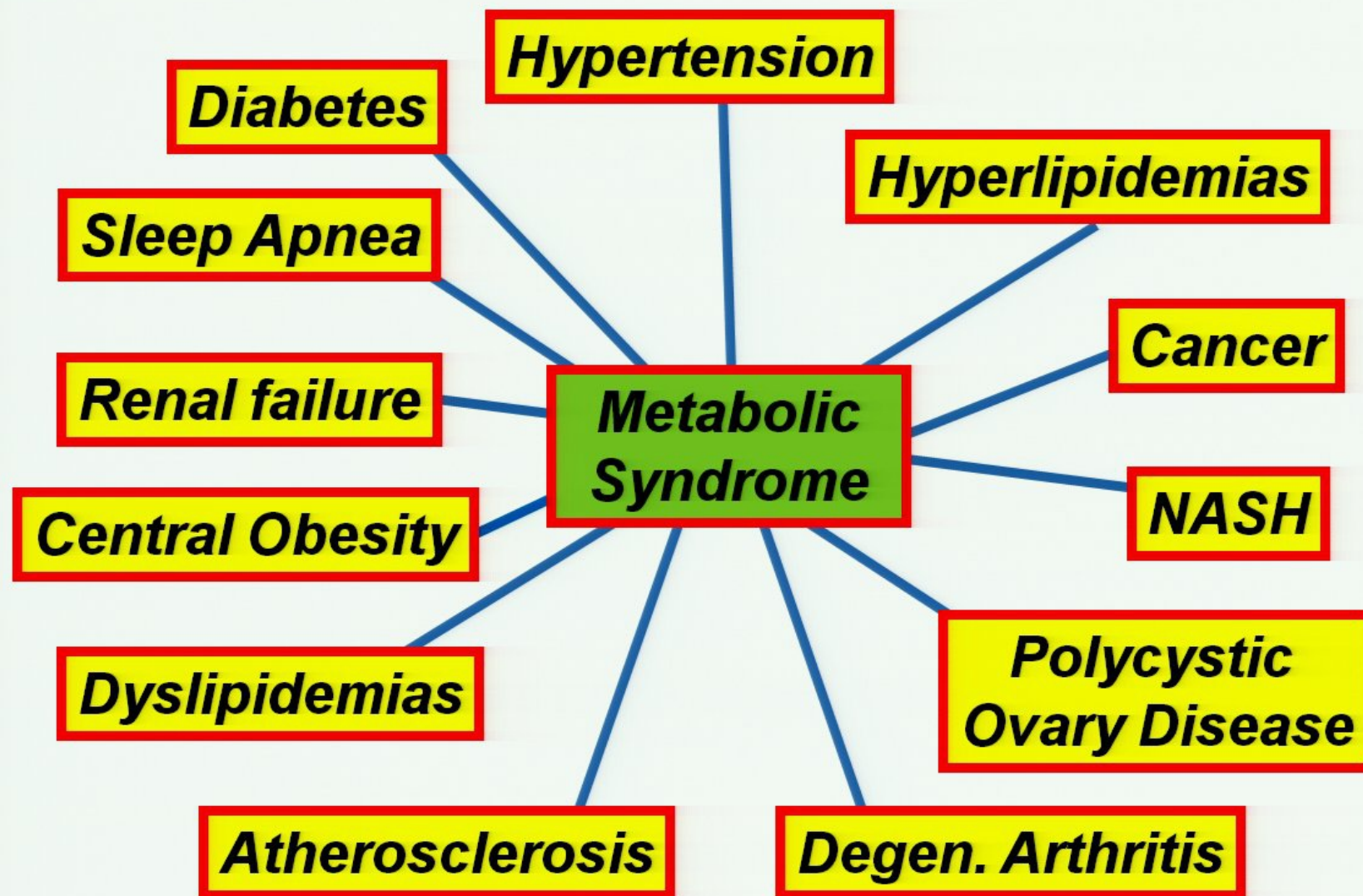
5 year followup: A Reduction in Cancers?



***p<0.001**

Christou et al. Ann Surg 2004;240:416-424

The effects of the surgery are far broader than the remission of T2DM



Conclusion #3: The gastric bypass produces full remission, not only of T2DM, but the entire metabolic syndrome.

OK, surgery works but isn't it dangerous?

Obese diabetic patients are not good surgical candidates...

The Bariatric Surgery Crisis: 2003

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- *Awful results*
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- *Bad press*
- *A tsunami of law suits*
- *2004: ECU Faculty developed a national Centers of Excellence Program, a non-profit Surgical Review Corporation, with very tough standards*

***ASMBS/SRC Data: 272 Hospitals, 495 Surgeons
>110,000 patients***

Hospital Mortality	76	0.14%
Operative Mortality at 30 days (76 + 89 = 165)	165	0.29%
Operative Mortality at <u>90 days</u> (76+89+31 = 196)	196	0.35%
Re-admissions	1,956	4.75%
Re-operations	887	2.15%

Now combined ASMBS/ACS 450 US Hospitals!

**TABLE 2. Mortality rates following
common operations in U.S. hospitals**

	Aortic Aneur	CABG	Craniot	Esophag Resect	Hip Replac	Panc	Ped. Heart Surger y
Number of Hospitals performing operation	2485	1036	1600	1717	3445	1302	458
National Average Mortality rate(%)	3.9	3.5	10.7	9.1	0.3	8.3	5.4
Average Hospital caseloads Median	30	491	12	5	24	8	4

[1] Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality. JAMA 2004;292, 847-851

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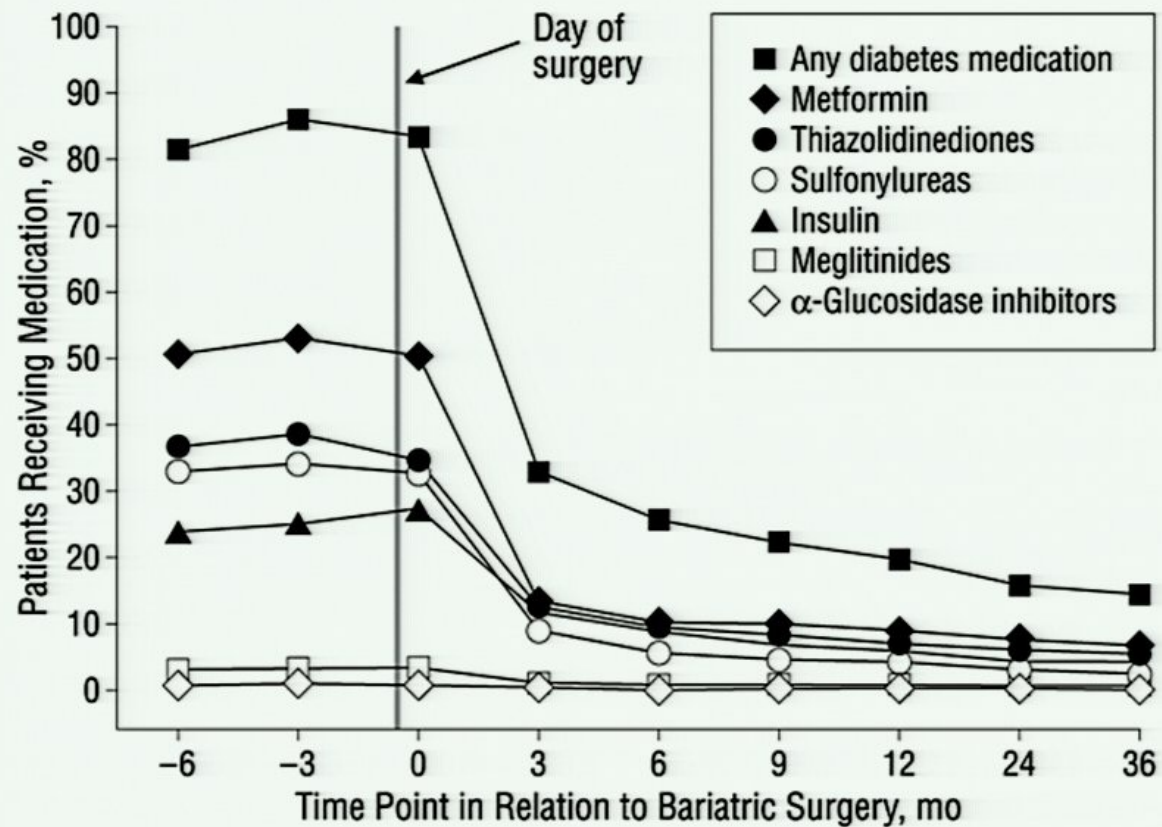
[1] Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality. JAMA 2004;292, 847-851

SRC: Bariatric Surgery Mortality 0.3% (55,567 patients)
106 Hospitals reporting Average Case Load: 312 cases/year
Cholecystectomy 0.3%; Delivery of First Baby 0.1%

**Conclusion #4: In tightly controlled
Centers of Excellence, bariatric
surgery can be delivered with the
safety of cholecystectomy**

But what about the cost?

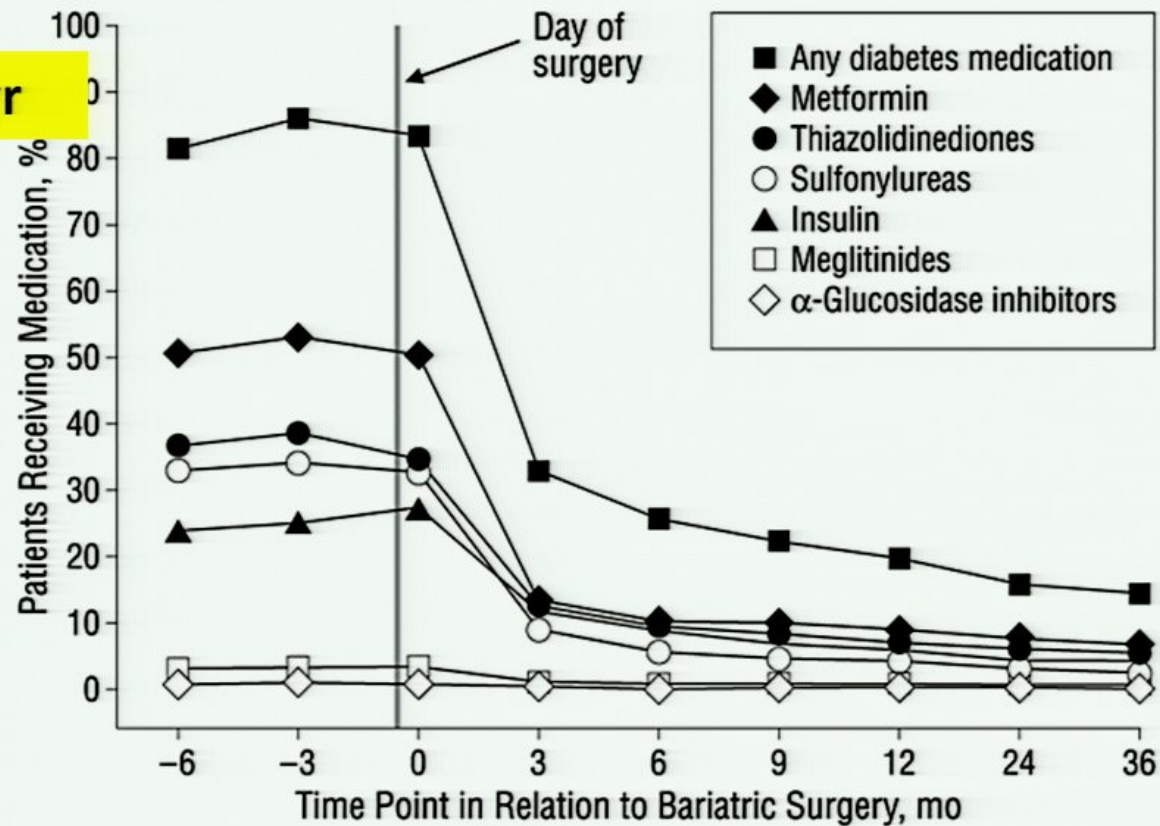
Use of diabetes medication before and after bariatric surgery by their primary care physicians



Makary, M. A. et al. Arch Surg 2010;145:726-731.

Use of diabetes medication before and after bariatric surgery by their primary care physicians

\$10,592/yr



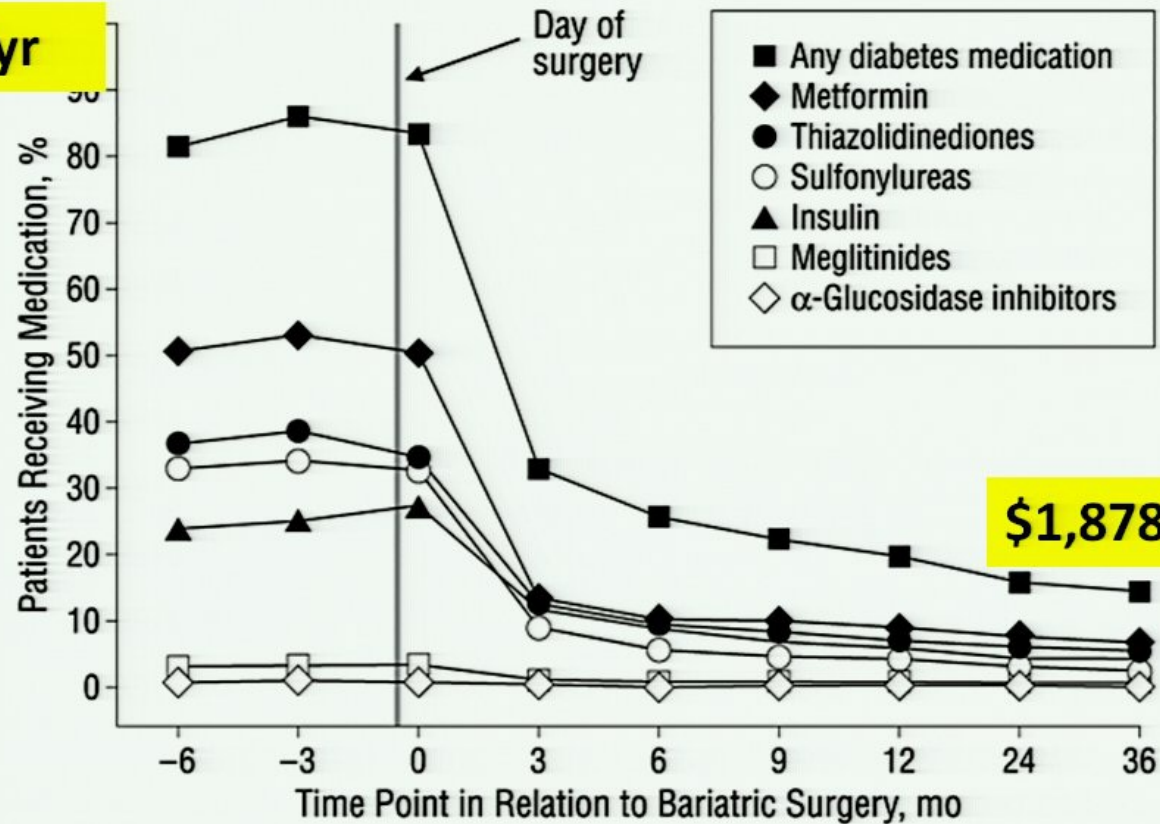
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Use of diabetes medication before and after bariatric surgery by their primary care physicians

\$10,592/yr



\$1,878/yr

Makary, M. A. et al. Arch Surg 2010;145:726-731.

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ARCHIVES OF
SURGERY

Bariatric surgery is cost-effective

- ***Average cost of bariatric surgery in the US:
\$18,000***

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Bariatric surgery is cost-effective

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- ***The costs of bariatric surgery are regained within 2 – 3 years.... which is why it is covered by every major carrier, Medicare and Medicaid***
- ***And these calculations do not include the savings in disability, unemployment insurance and taxes paid by these recovered patients***

***Conclusion #5:
Bariatric surgery is cost-effective***

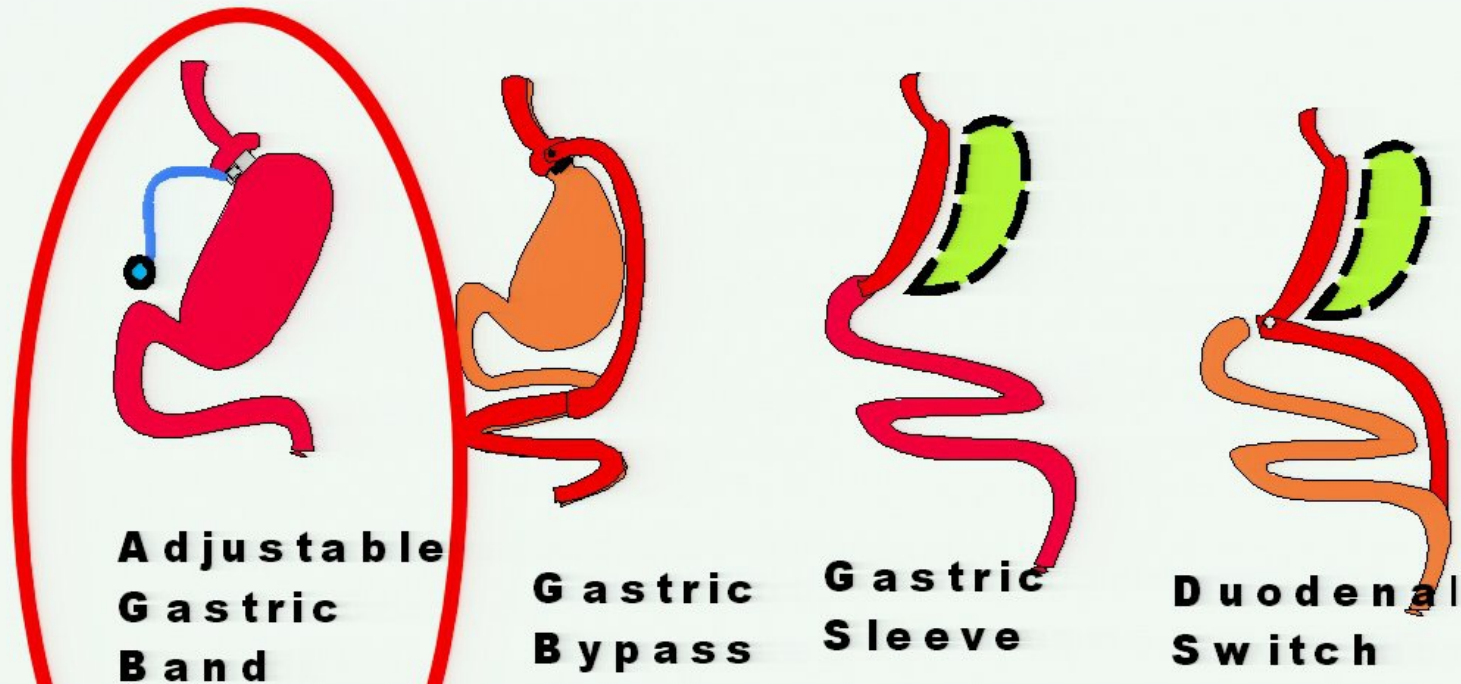
***Those are remarkable outcomes.
Any explanations regarding
mechanisms?***

***Those are remarkable outcomes.
Any explanations regarding
mechanisms?***

***Is the remission of T2DM due to
weight loss?***

THE FOUR CURRENTLY ACCEPTED BARIATRIC OPERATIONS

Meta-analysis: All articles in English, 1990 – 2006,
621 studies, 888 treatment arms, 135,246 patients



XS WT Loss	46.2%	57.9%	? 60%	63.6%
Stop T2DM	56.7%	80.3%	? 60%	95.1%

*Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge, I.
Meta-analysis of Bariatric Surgery and Diabetes, Am J Med (2009)122: 248 - 256*

***Is the remission of T2DM
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- ***Banding, an operation that is an enforced diet, produces a 56.7% remission of T2DM***

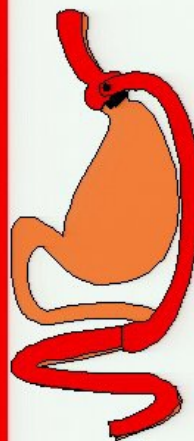
Is the remission of T2DM due to weight loss?

- ***Bariatric patients do lose a lot of weight***
- ***Weight loss is a proven method for the improvement in T2DM***
- ***Banding, an operation that is an enforced diet, produces a 56.7% remission of T2DM***
- ***But the remission may take one to three years, parallel with weight loss***

**THESE THREE OPERATIONS REVERSE T2DM
IN A MATTER OF DAYS: It's not just weight loss...**



**Adjustable
Gastric
Band**



**Gastric
Bypass**



**Gastric
Sleeve**



**Duodenal
Switch**

XS WT Loss	46.2%	57.9%	? 55%	63.6%
Stop T2DM	56.7%	80.3%	? 80%	95.1%

*Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge, I.
Meta-analysis of Bariatric Surgery and Diabetes, Am J Med (2009)122: 248 - 256*



Has anyone performed metabolic surgery on lean diabetic patients?

***DUODENAL-JEJUNAL LAP BYPASS
IN LEAN PATIENTS WITH DIABETES***

Ramos A, Galvao Neto M, Galvao M.

Patients	Follow-up	Fasting Glycemia Pre-op	Fasting Glycemia Post-op
1. RG	7m	216	98
2. CD	7m	168	110
3. MC	6m	157	79
4. MM	5m	148	82
5. RD	2m	225	94
6. JG	1m	173	92

Ramos A, Galvao Neto M, Galvao M.

DUODENAL-JEJUNAL LAP BYPASS IN LEAN PATIENTS WITH DIABETES

Ramos A, Galvao Neto M, Galvao M.

Patients	Follow-up	HbA1c Pre-op	HbA1c Post-op
1. RG	7m	8.6	6.2
2. CD	7m	7.5	6.0
3. MC	6m	8.2	5.8
4. MM	5m	7.8	6.3
5. RD	2m	8.2	7.6
6. JG	1m	8.7	7.9

Ramos A, Galvao Neto M, Galvao M.

Dr M. Lakdawala M.S. India:
Lean Diabetic Patients (@ 6 months after DJB)

	Pre-surgery N=3	Post surgery 6 months
BMI	1. 27.5 2. 28 3. 29.5	27.5 27 29
HbA1C	1. 9 2. 10.4 3. 9.5	5.1 6.3 6.0
PP Insulin	1. 240 2. 232 3. 244	59.5 56.5 50.0
FBS	1. 128 2. 155 3. 162	95 92 90
PPBS	1. 265 2. 244 3. 275	104 134 124

***The remission of T2DM is not
primarily due to weight loss***

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- *Full remission occurs without significant weight loss*

The remission of T2DM is not primarily due to weight loss

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- ***The speed of the remission in a matter of days***

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- ***The remission rates of the band (56.7%) are far below of the operations that exclude gut***

The remission of T2DM is not primarily due to weight loss

- ***Full remission occurs without significant weight loss***
- ***The speed of the remission in a matter of days***
- ***The remission rates of the band (56.7%) are far below of the operations that exclude gut***
 - ***80.3% with the gastric bypass and***
 - ***95.1% with the duodenal switch***

***Conclusion #6: Weight loss plays a role but
there must also be a factor from the gut that
causes diabetes***

Conclusion #6: Weight loss plays a role but there must also be a factor from the gut that causes diabetes

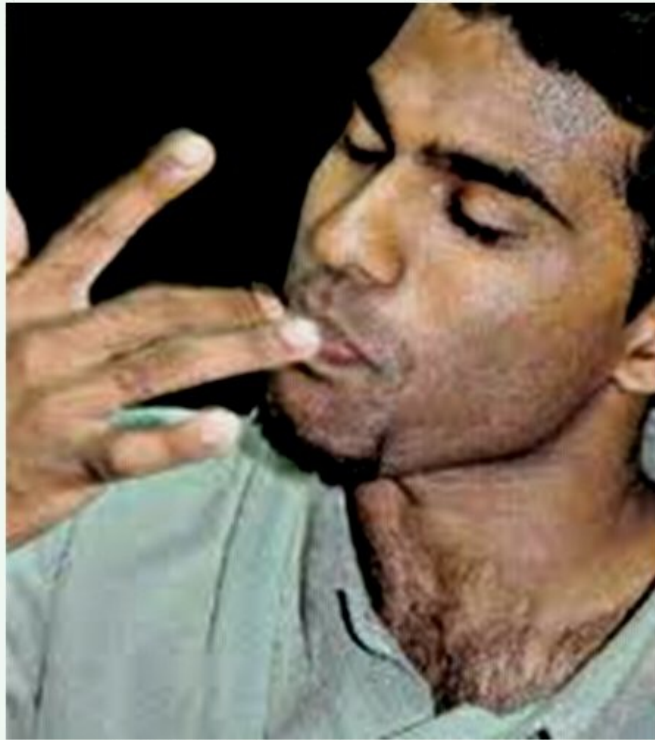
Could T2DM be caused by aberrant signals from the gut?

Hmmmm.
Let's look at T2DM again...

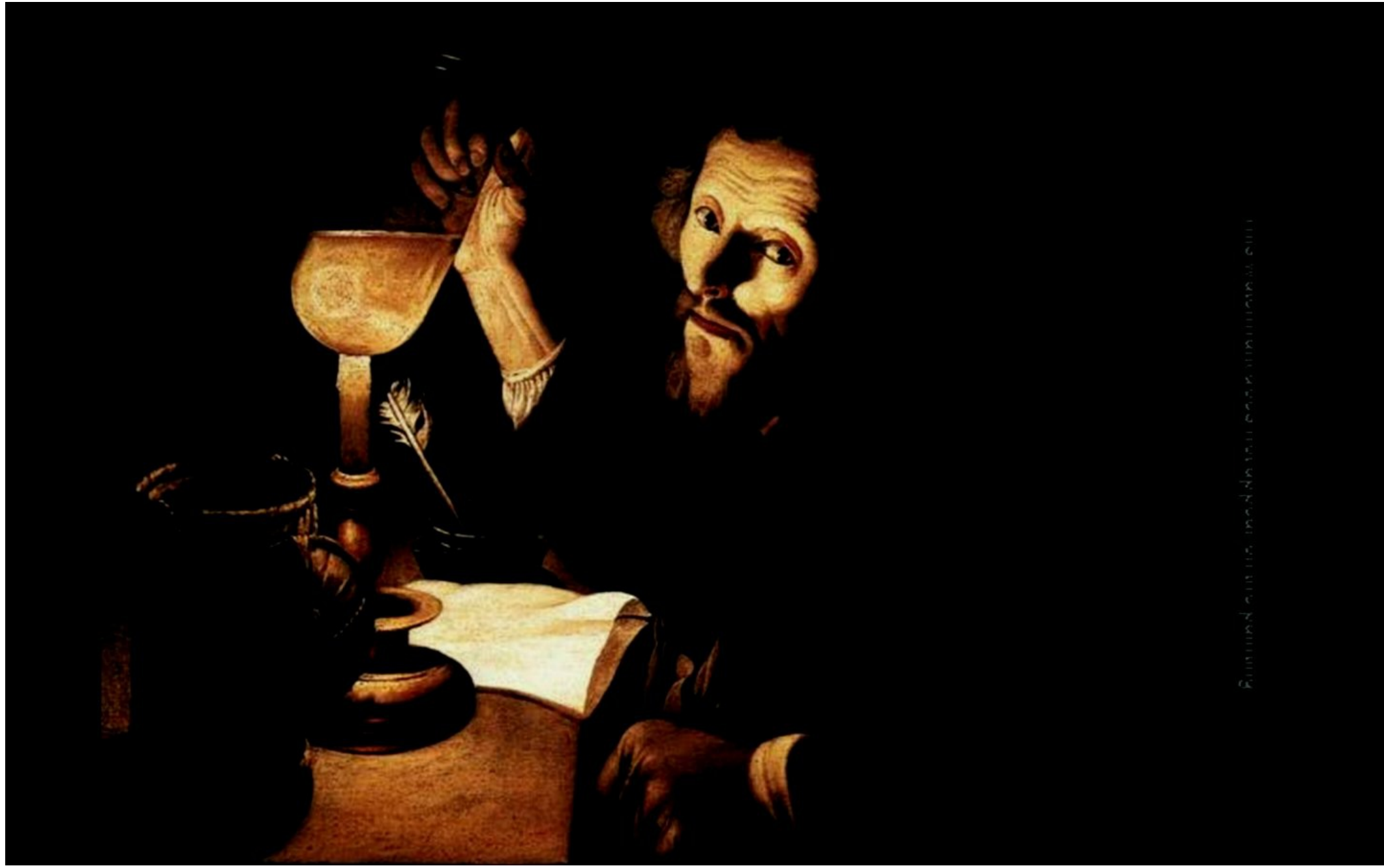
***With diabetes,
it's always been about sugar***



In 1552 BC, ancient Hindu writings first described black flies and ants congregating around the sweet urine of unwell individuals.



In 400 BC, the Indian physician Sushruta described the urine's sweet taste, and for hundreds of years this was the foundation of diagnosis



Caravaggio, "Boy with a Basket of Fruit" (1593-1594)

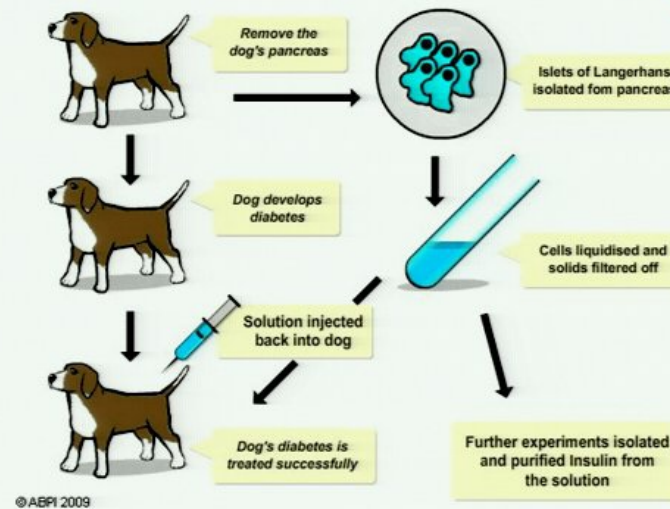
And even today, we depend on measurement of glucose to make a diagnosis of diabetes

- ***Fasting Blood Sugar***
- ***Hb1Ac (Glycosylated hemoglobin)***
- ***Postprandial Blood Sugar***
- ***Glucose Tolerance Test***
- ***Glucose Clamp***



THE MIRACLE OF INSULIN

December 30, 1921



An extract from the islets in a dog's pancreas, "insulin", reverses the fatal high levels of glucose in a diabetic child

Insulin reversed the hyperglycemia!!

For 15 years, only one type of diabetes, i.e. manifested by hyperglycemia was recognized.

Insulin was adopted as the most effective treatment for both diseases even though they are fundamentally different.

***The distinction between
type 1 diabetes and type 2 diabetes
was not evident until the publication by
Harold Percival (Harry) Himsworth,
in January 1936 (15 years later)***

***The distinction between
type 1 diabetes and type 2 diabetes
was not evident until the publication by
Harold Percival (Harry) Himsworth,
in January 1936 (15 years later)***

***By that time, insulin was already widely
adopted as the treatment for diabetes.....***

Two forms of diabetes:

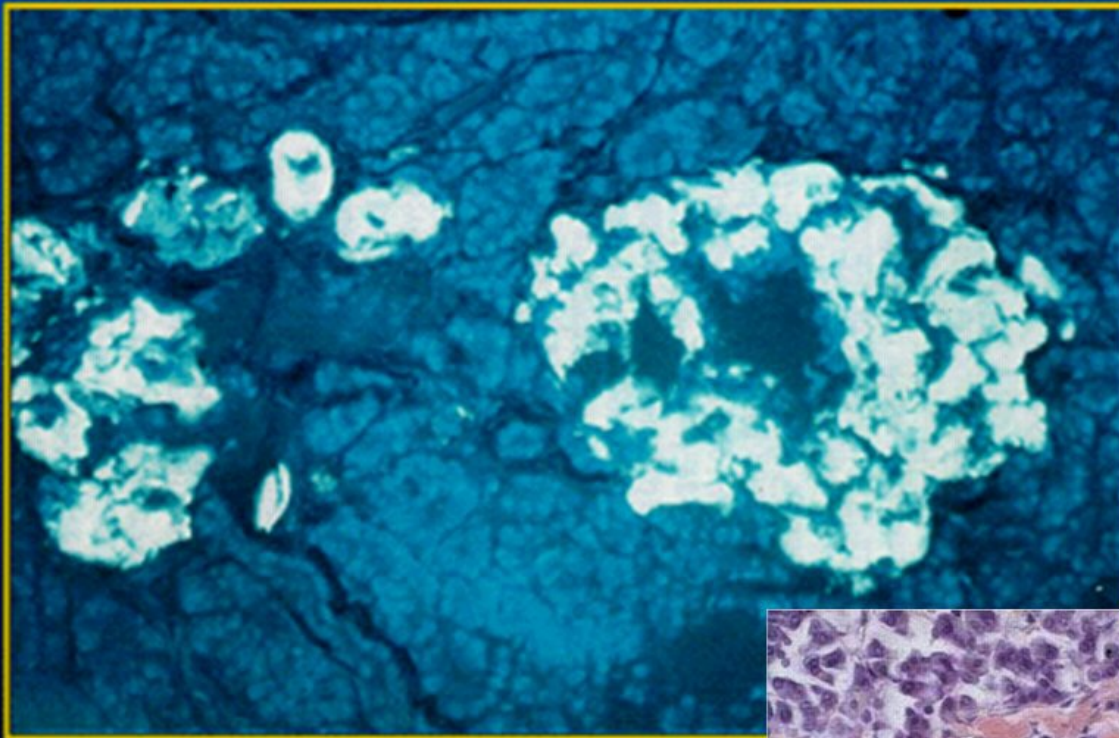
Two forms of diabetes:

- ***Type 1: pancreatic islets are destroyed by immune response after a viral infection. Unable to produce insulin: high glucose and low insulin***

Two forms of diabetes:

- ***Type 1: pancreatic islets are destroyed by immune response after a viral infection. Unable to produce insulin: high glucose and low insulin***
- ***Type 2: cause uncertain. High glucose and high insulin***

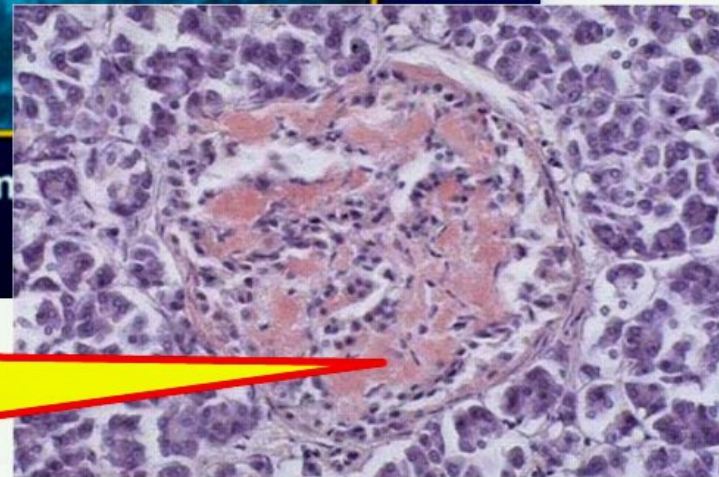
Amyloid Deposits in Pancreatic Islets in Type 2 Diabetes



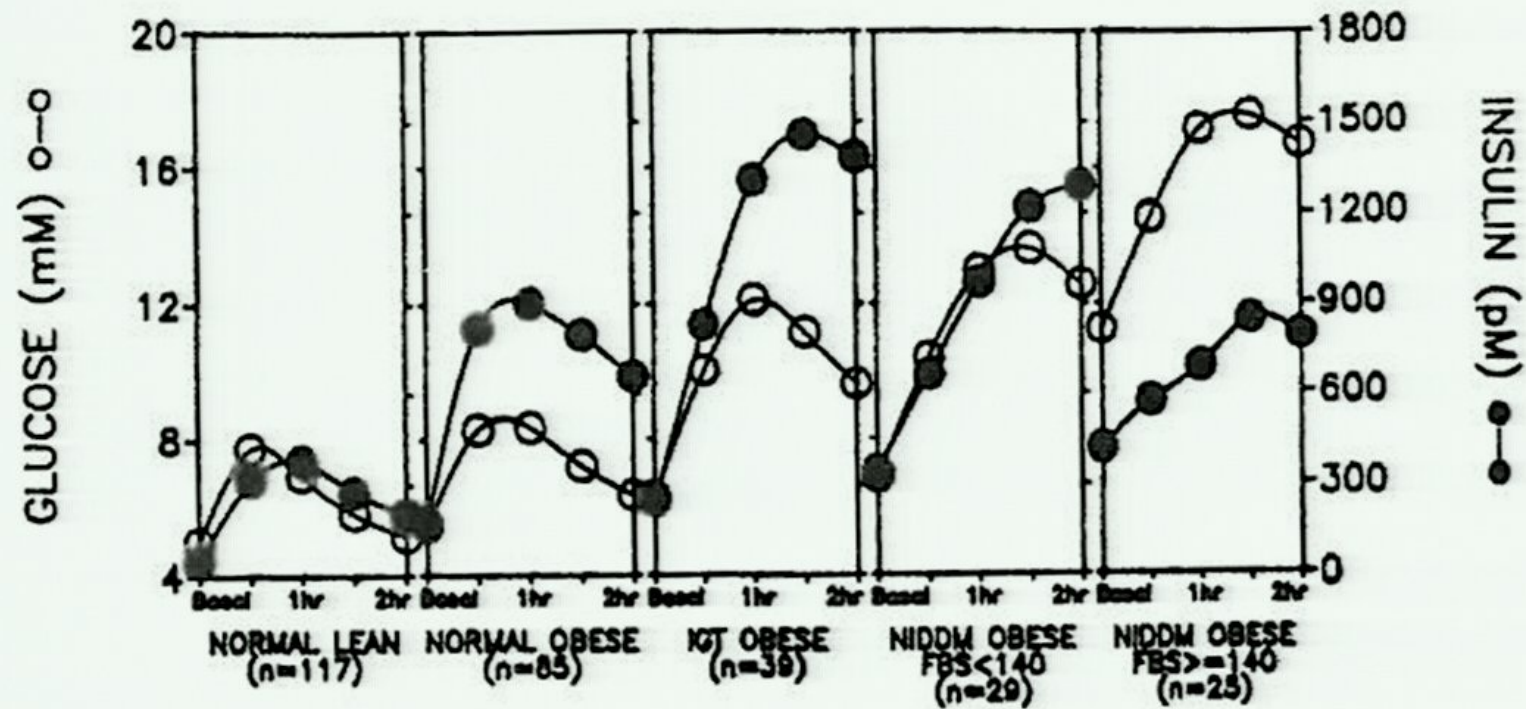
Amyloid deposits in pancreatic islets of human

Verchere C

**Amyloid deposits in
advanced T2DM**



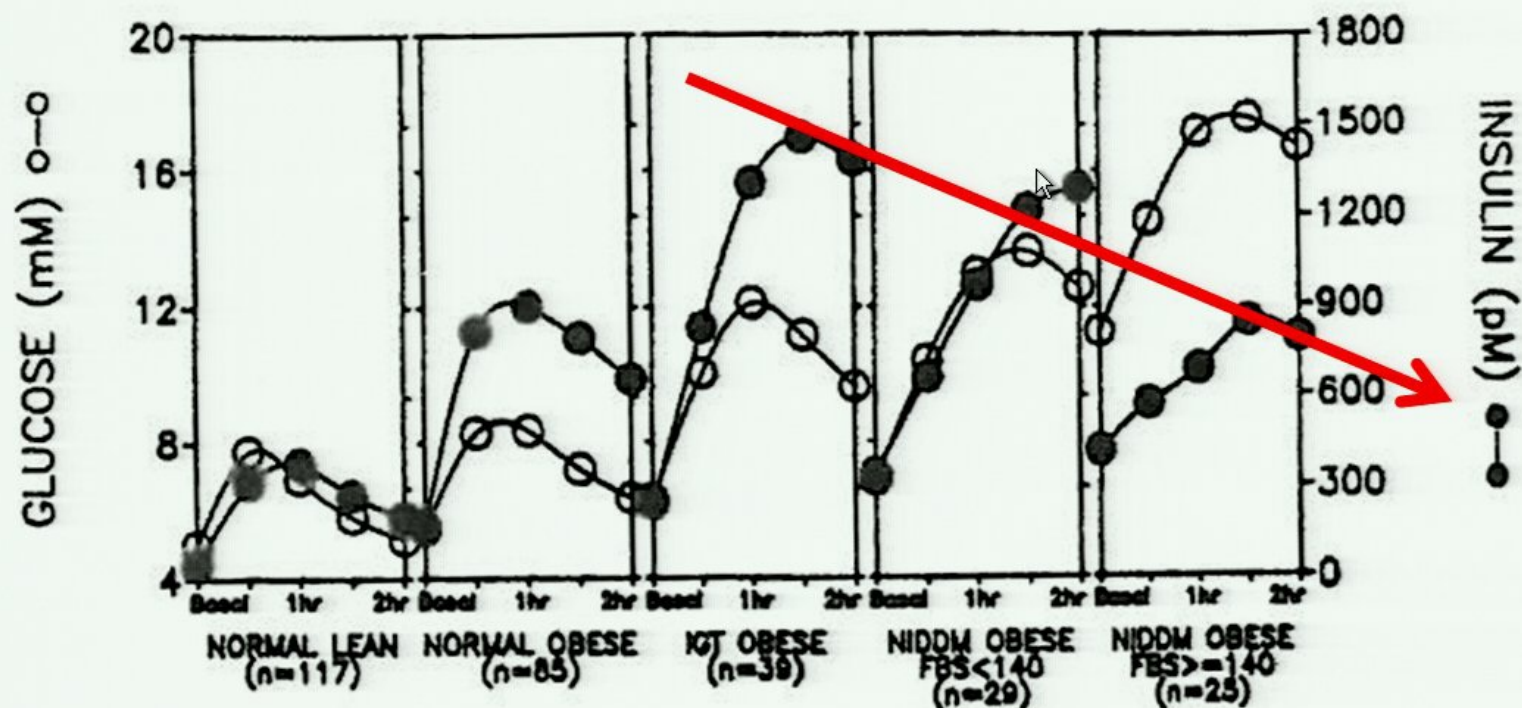
ORAL GLUCOSE TOLERANCE TEST



Pories, et al. Surgical treatment of obesity and its effect on diabetes. 10 year follow-up. *Am. J. Clin. Nutr.* 55: 582S-585S, 1992

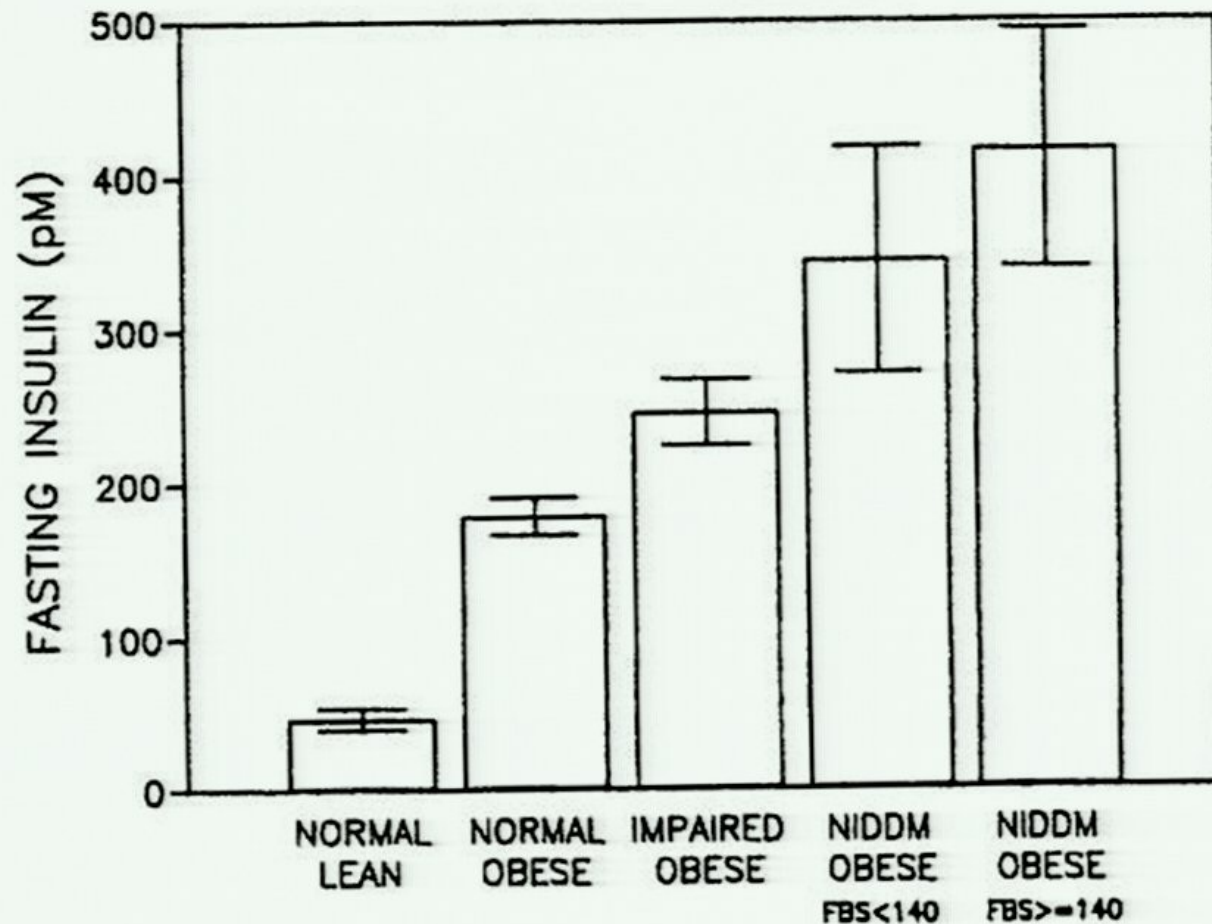
Yes, maximum insulin secretion falls with progression of T2DM

ORAL GLUCOSE TOLERANCE TEST



Pories, et al. Surgical treatment of obesity and its effect on diabetes. 10 year follow-up. *Am. J. Clin. Nutr.* 55: 582S-585S, 1992

T2DM patients are very hyperinsulinemic



Pories, et al. Surgical treatment of obesity and its effect on diabetes. 10 year follow-up. *Am. J. Clin. Nutr.* 55: 582S-585S, 1992

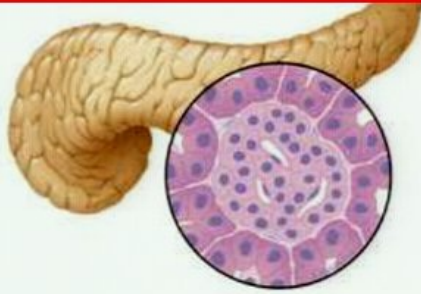
Type 2 diabetic patients have high levels of insulin. How can we explain that surprising finding?

Current view:

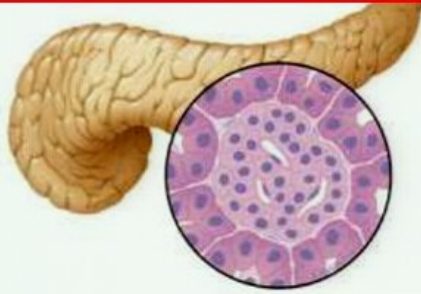
Hyperglycemia due to

Peripheral Insulin Resistance

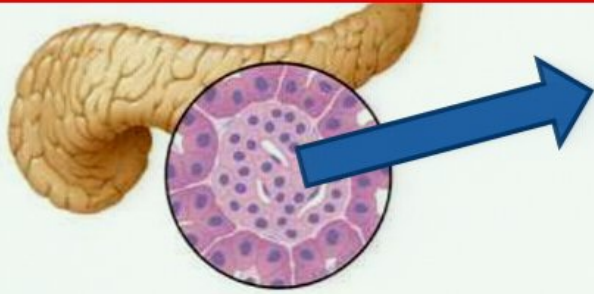
***Current view:
Hyperglycemia due to
Peripheral Insulin Resistance***



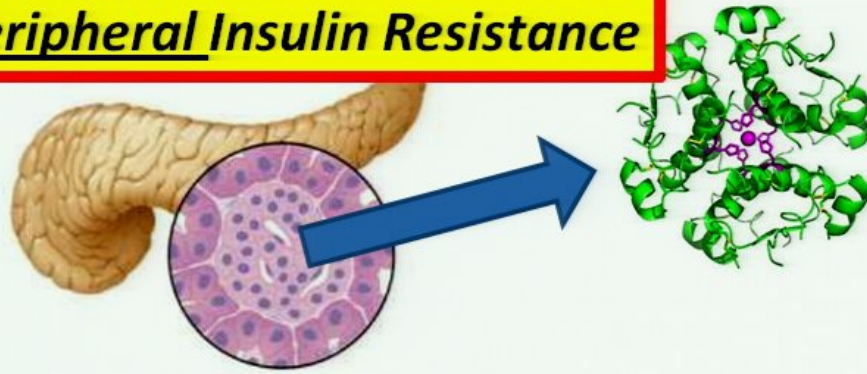
Current view:
Hyperglycemia due to
Peripheral Insulin Resistance



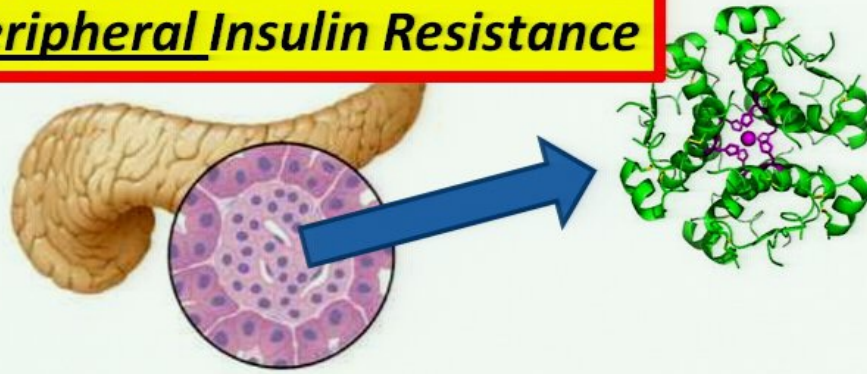
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Hyperglycemia due to
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Current view:
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Peripheral Insulin Resistance



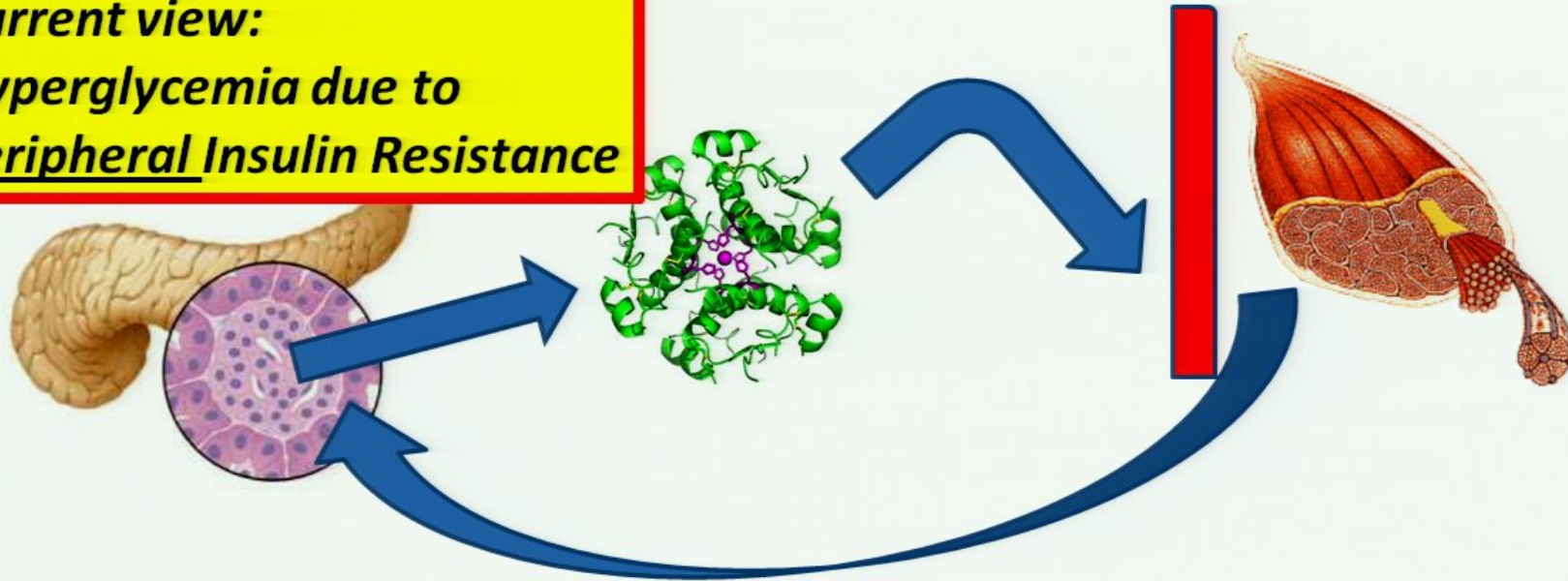
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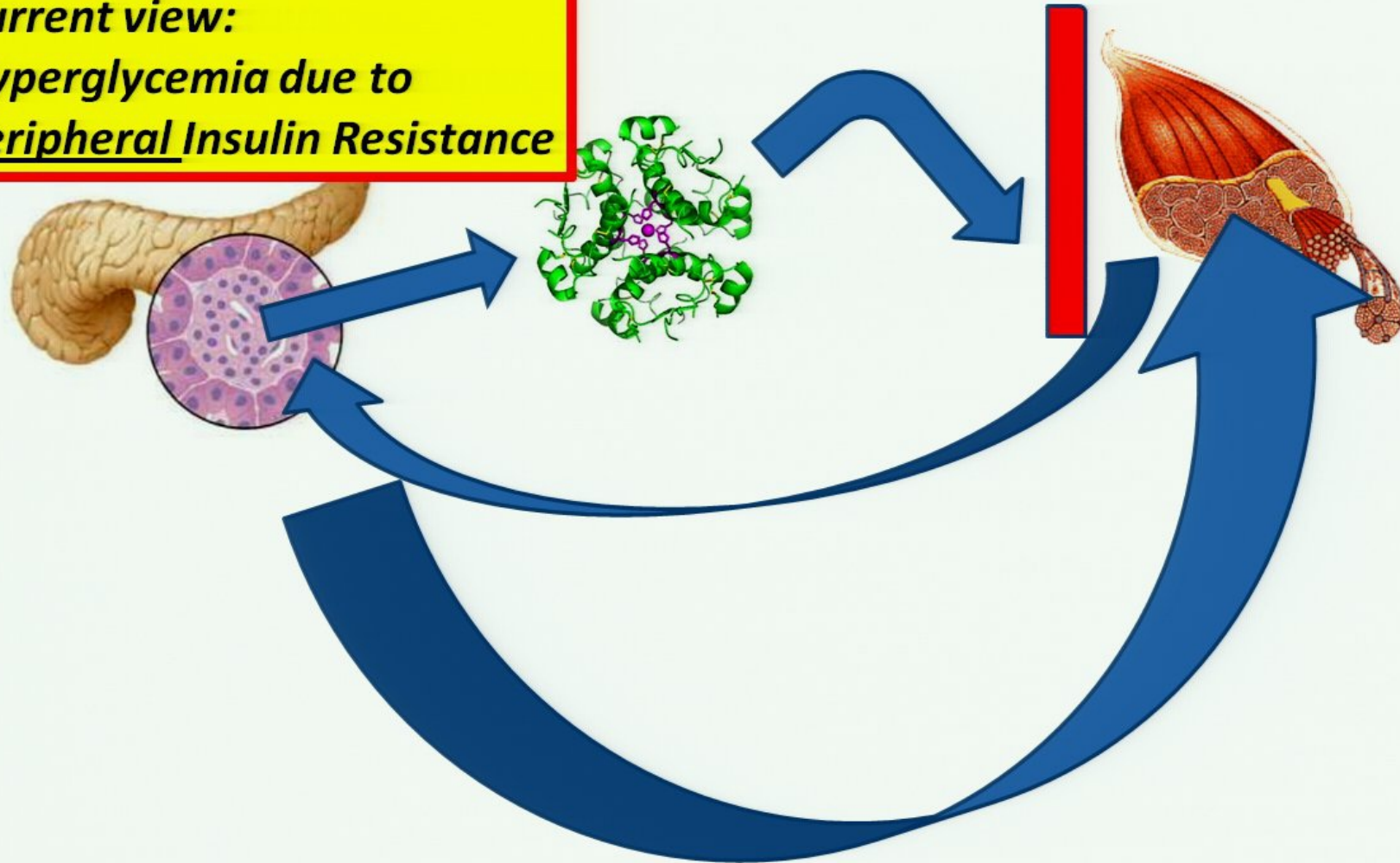
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Hyperglycemia due to
Peripheral Insulin Resistance



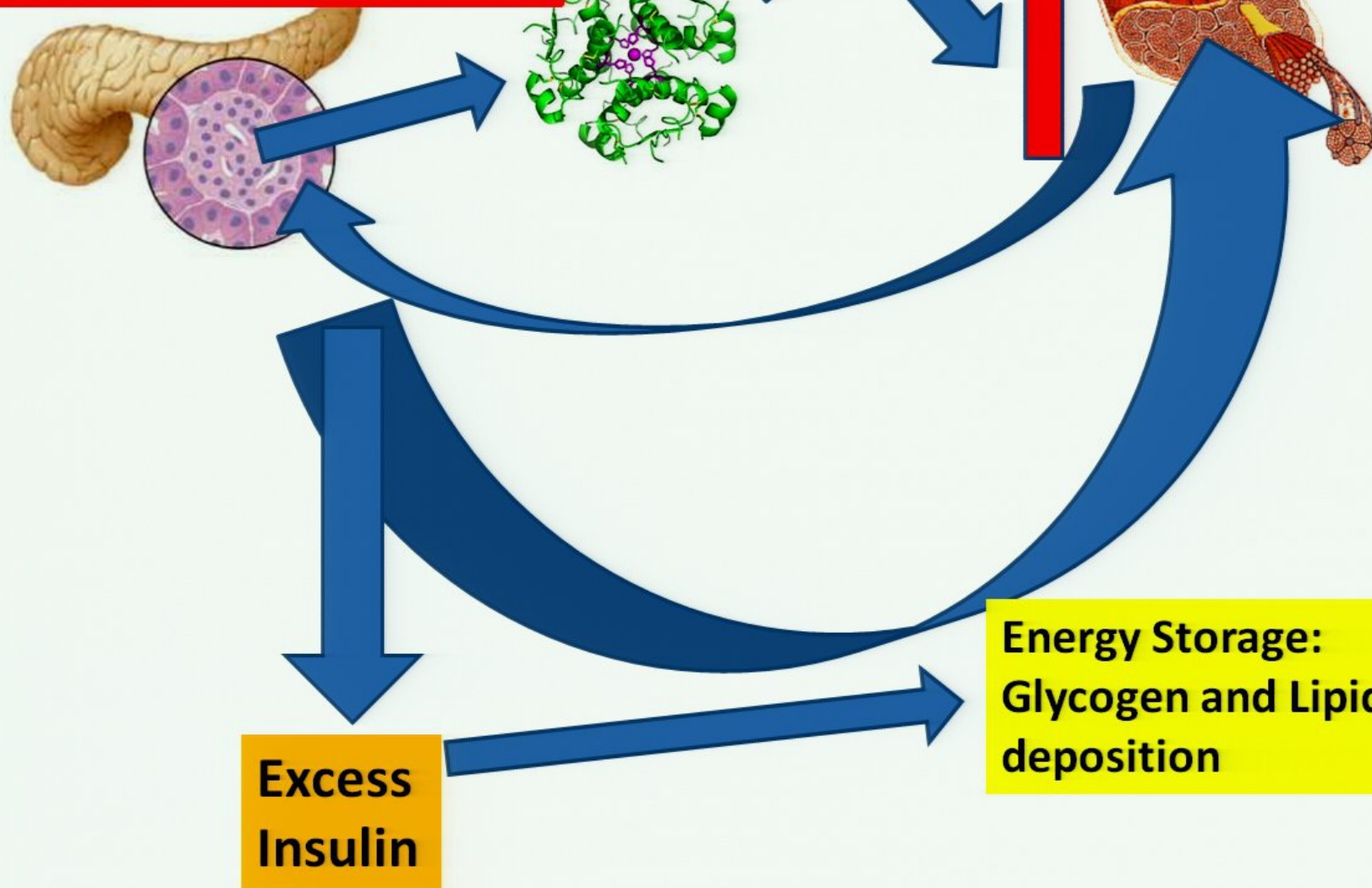
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Hyperglycemia due to
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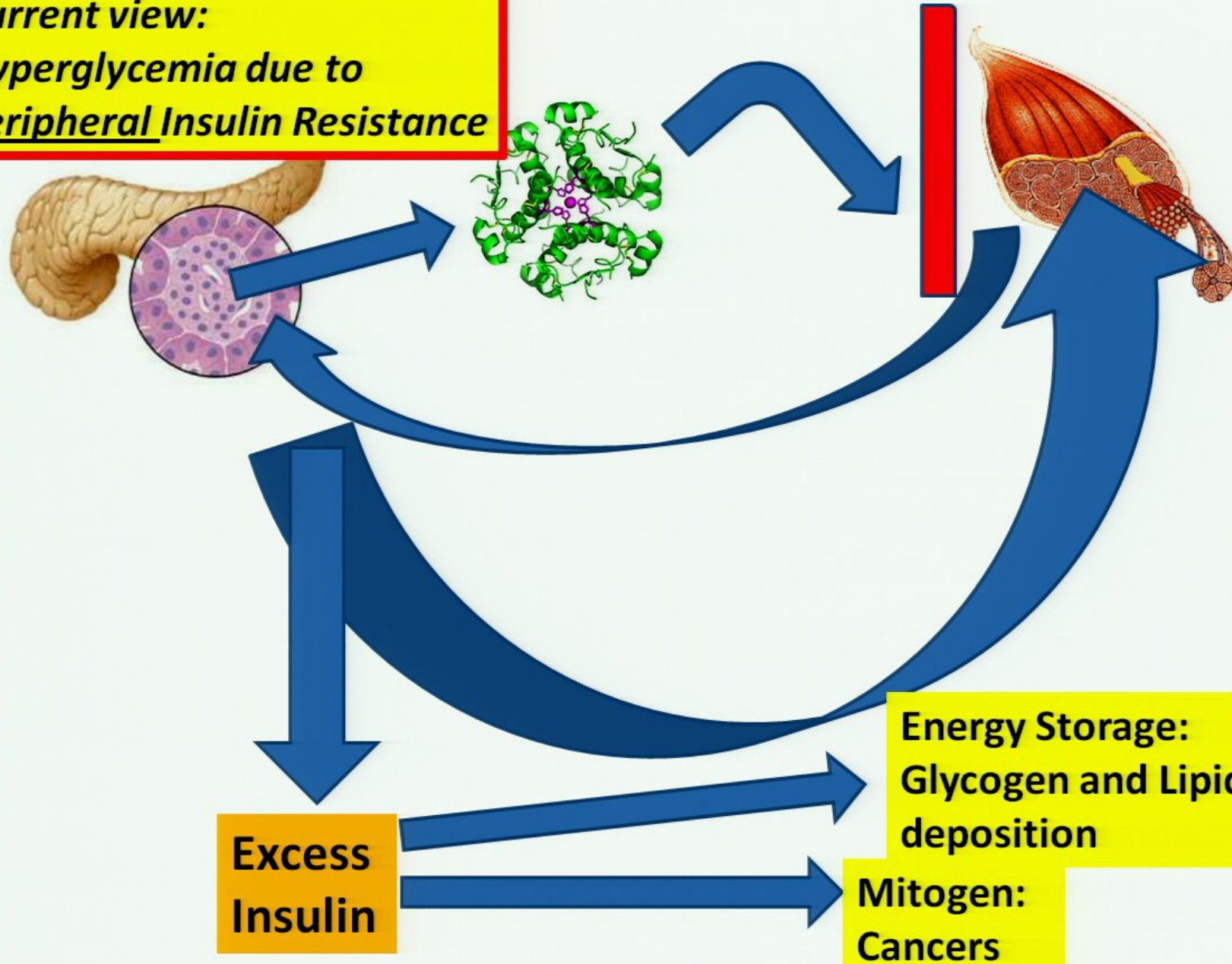
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**Current view:
Hyperglycemia due to
Peripheral Insulin Resistance**

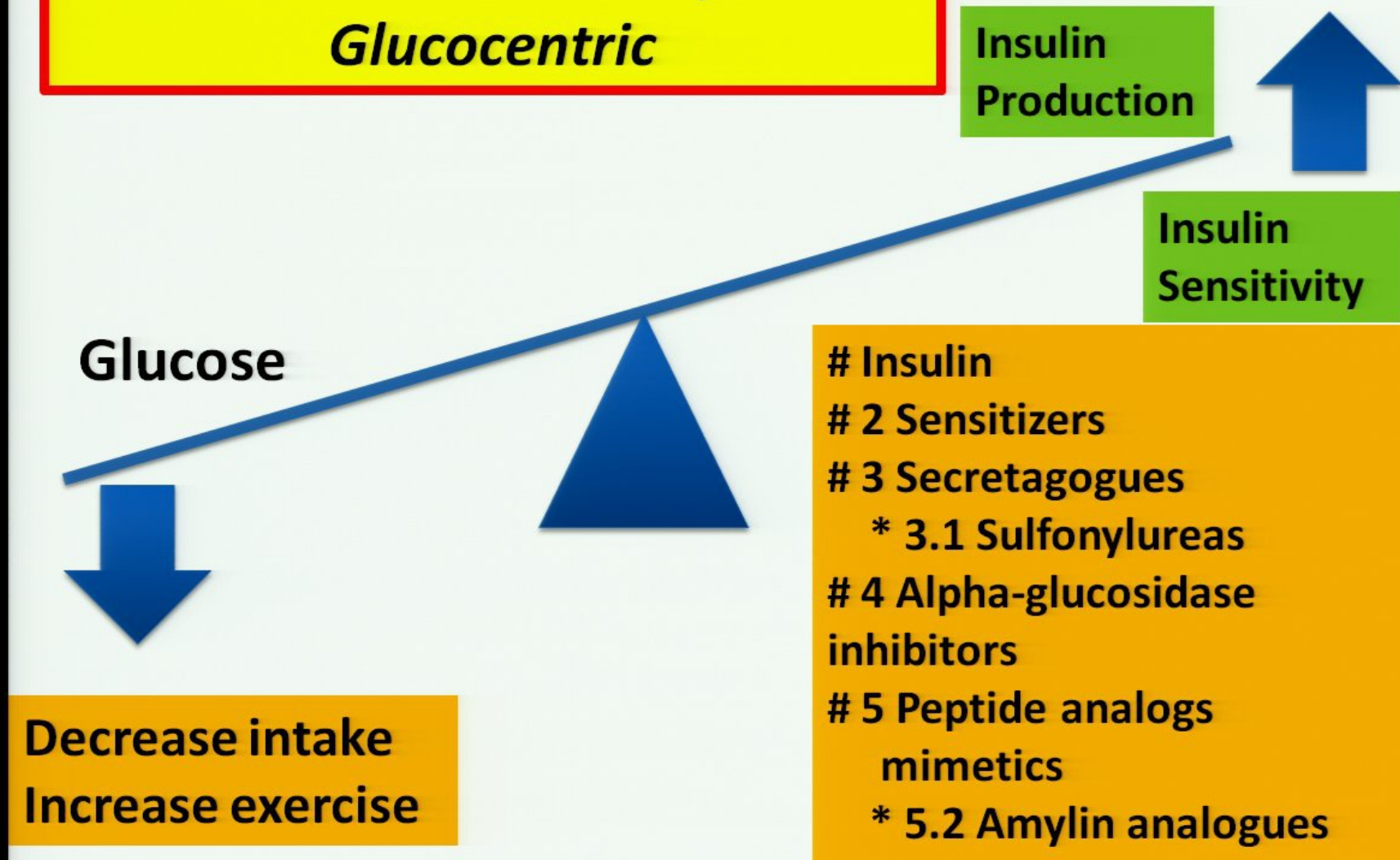


**Current view:
Hyperglycemia due to
Peripheral Insulin Resistance**



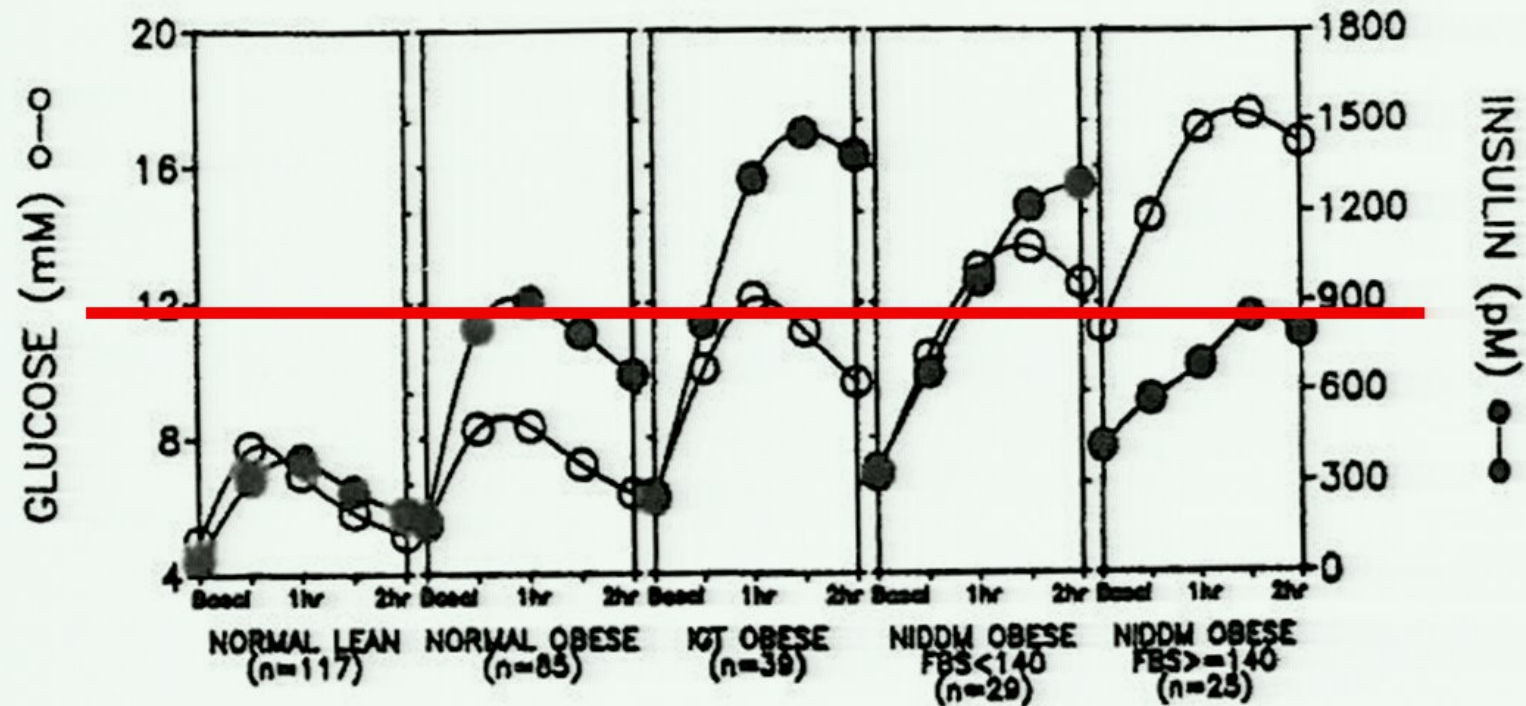
The current Treatment of T2DM

Glucocentric



BUT....

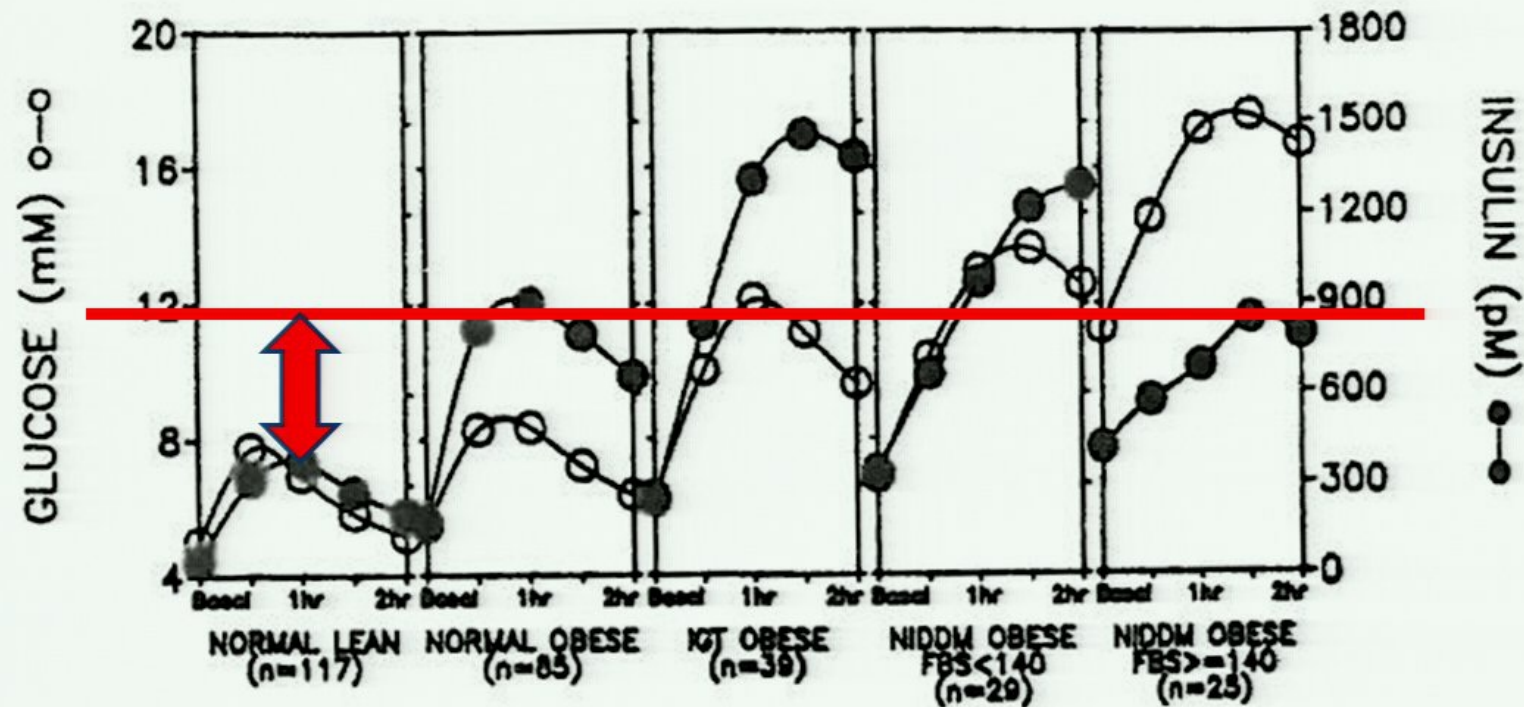
ORAL GLUCOSE TOLERANCE TEST



Pories, et al. Surgical treatment of obesity and its effect on diabetes. 10 year follow-up. *Am. J. Clin. Nutr.* 55: 582S-585S, 1992

BUT it's still higher than insulin secretion in a normal person

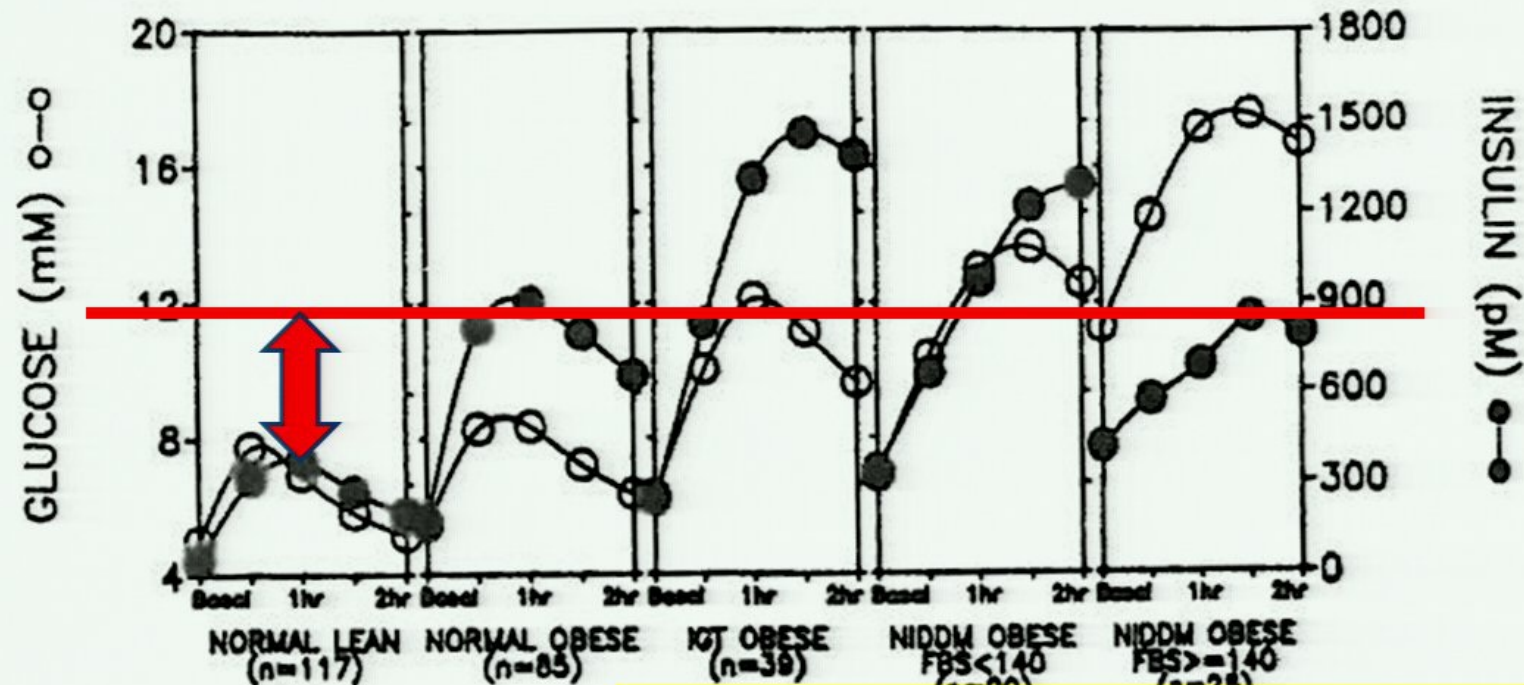
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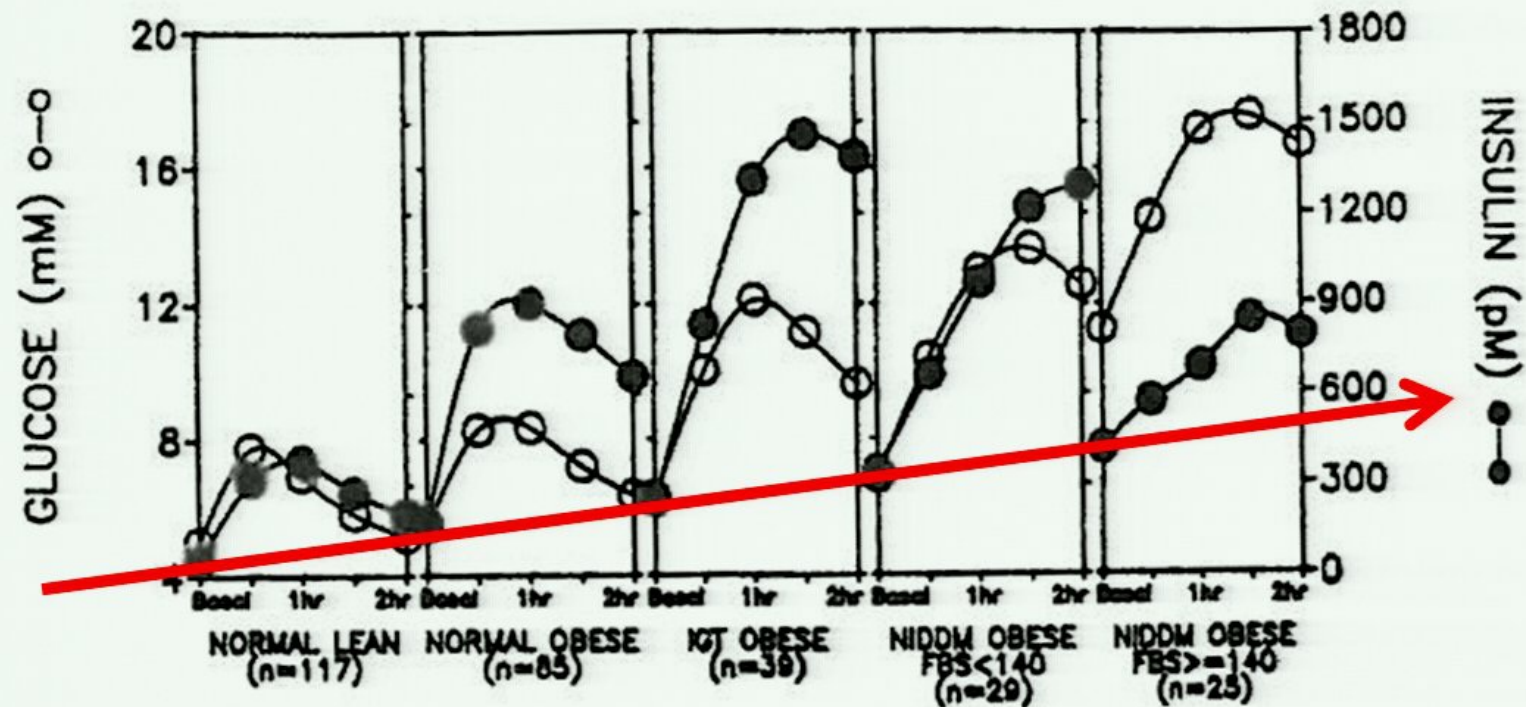


Even in advanced diabetes, insulin secretion is still higher than normal

Pories, et al. Surgical treatment of obesity and its effect on diabetes. 10 year follow-up. *Am. J. Clin. Nutr.* 55: 582S-585S, 1992

Is the problem the rise in basal secretion?

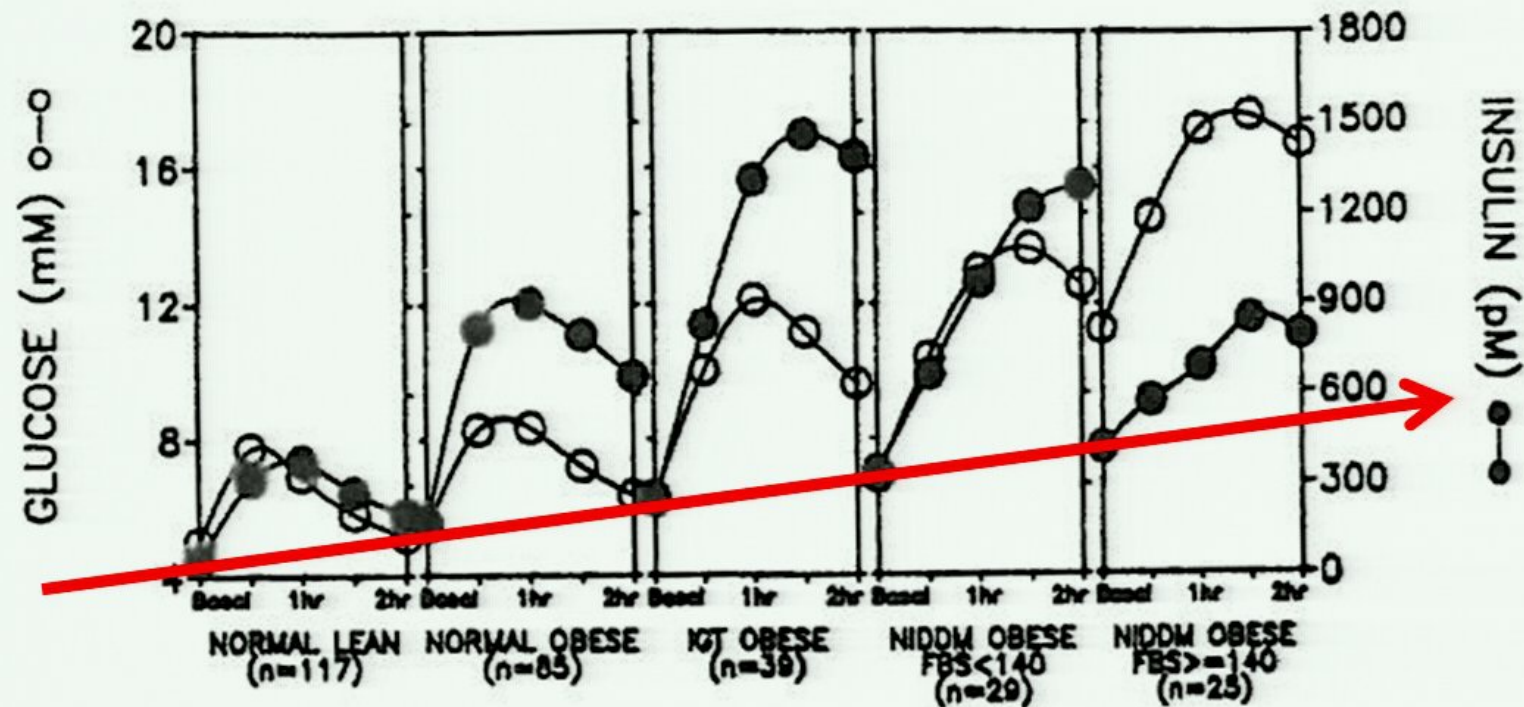
ORAL GLUCOSE TOLERANCE TEST



Pories, et al. Surgical treatment of obesity and its effect on diabetes. 10 year follow-up. *Am. J. Clin. Nutr.* 55: 582S-585S, 1992

Is the problem the rise in basal secretion?

ORAL GLUCOSE TOLERANCE TEST



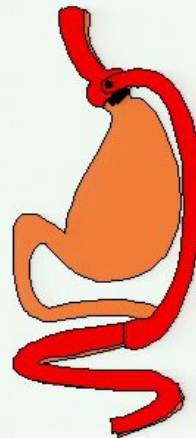
Conclusion #7: Even in advanced T2DM, patients secrete more insulin than normal individuals. They even have high basal, fasting insulin levels

***Can we get any more information
from T2DM outcomes after surgery?***

***The Remission of T2DM is "dose-related"
to the degree of reduction of contact
between food and the gut***



**A d j u s t a b l e
G a s t r i c
B a n d**



**G a s t r i c
B y p a s s**



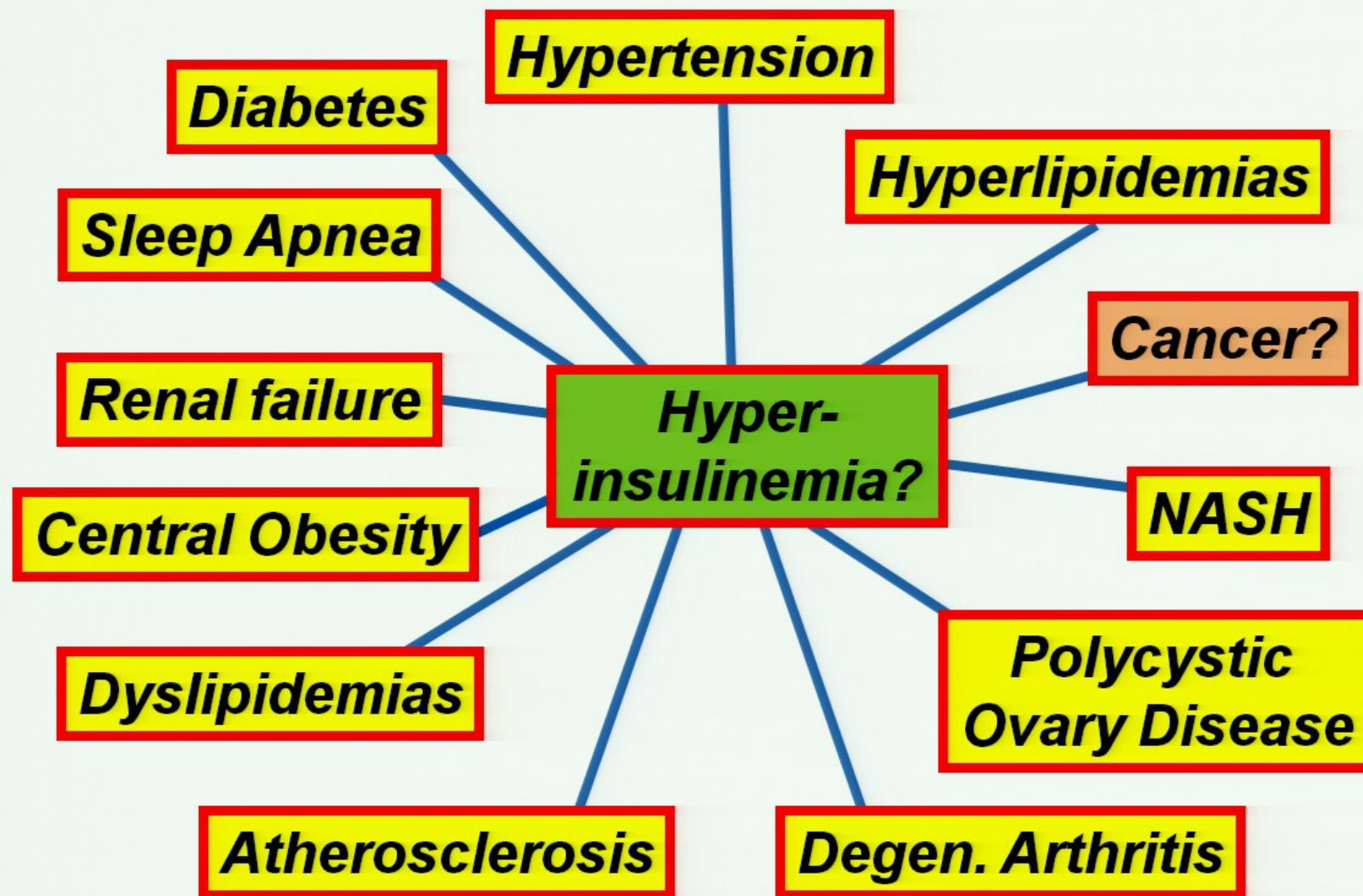
**G a s t r i c
S l e e v e**



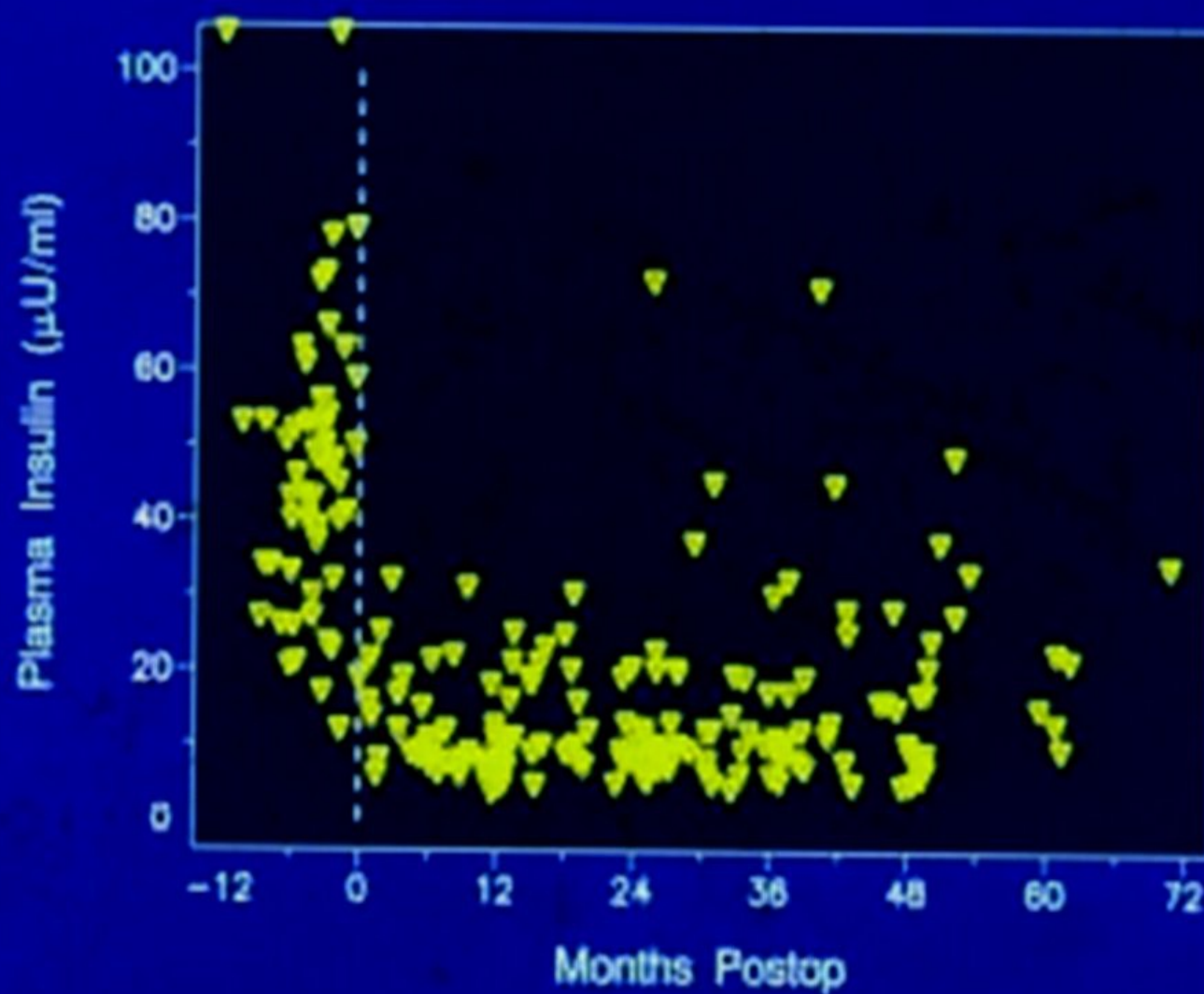
**D u o d e n a l
S w i t c h**

<i>XS WT Loss</i>	46.2%	57.9%	? 58.0%	63.6%
<i>Stop T2DM</i>	56.7%	80.3%	? 80.0%	95.1%

*Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge, I.
Meta-analysis of Bariatric Surgery and Diabetes, Am J Med (2009)122: 248 - 256*



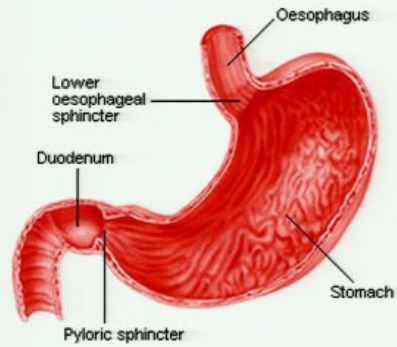
RESPONSE OF INSULIN LEVELS TO THE GGB



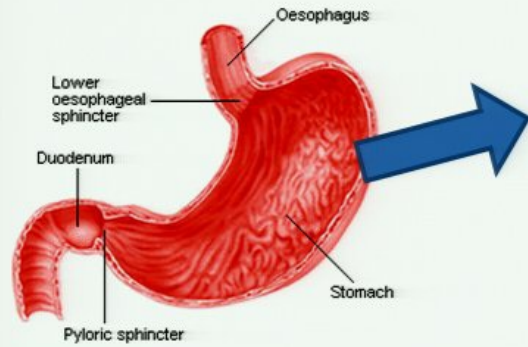
Conclusion #8: *The remission of T2DM and, indeed, the remission of the metabolic syndrome follows exclusion of parts of the gut. The gut, therefore, must play a role in the development of T2DM.*

***Proposed view: Hyperglycemia
due to XS insulin secretion***

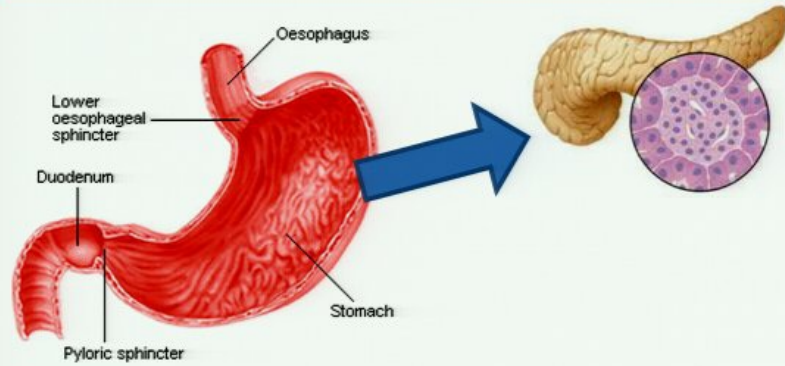
***Proposed view: Hyperglycemia
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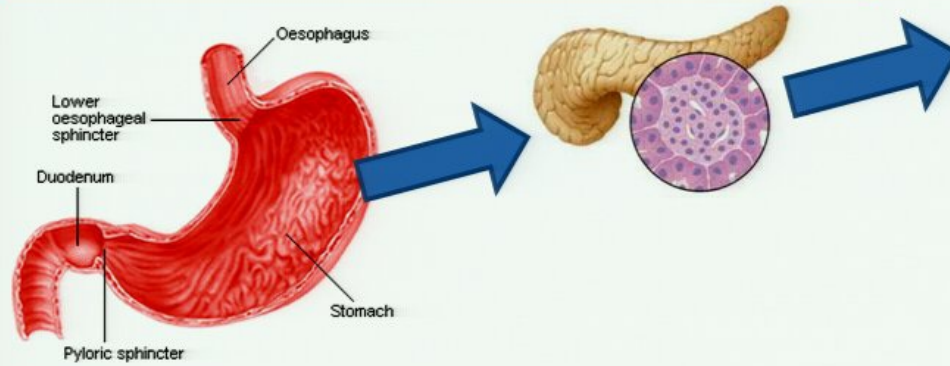
***Proposed view: Hyperglycemia
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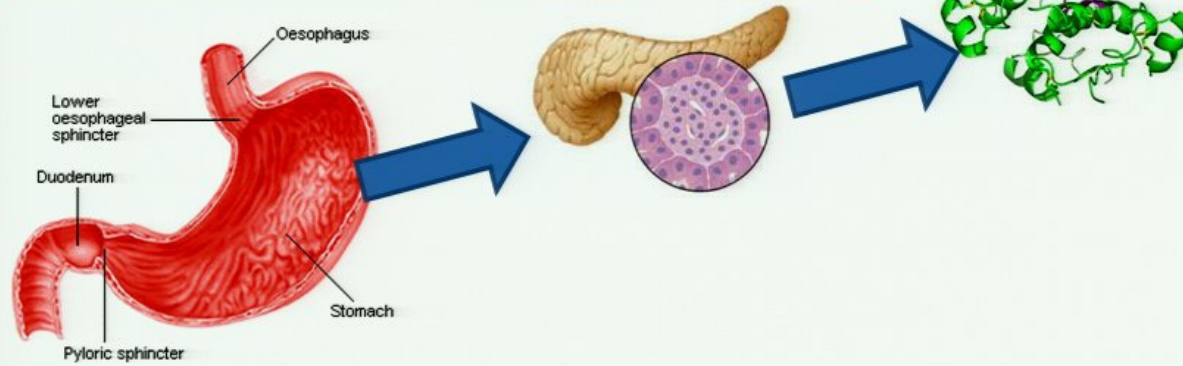
***Proposed view: Hyperglycemia
due to XS insulin secretion***



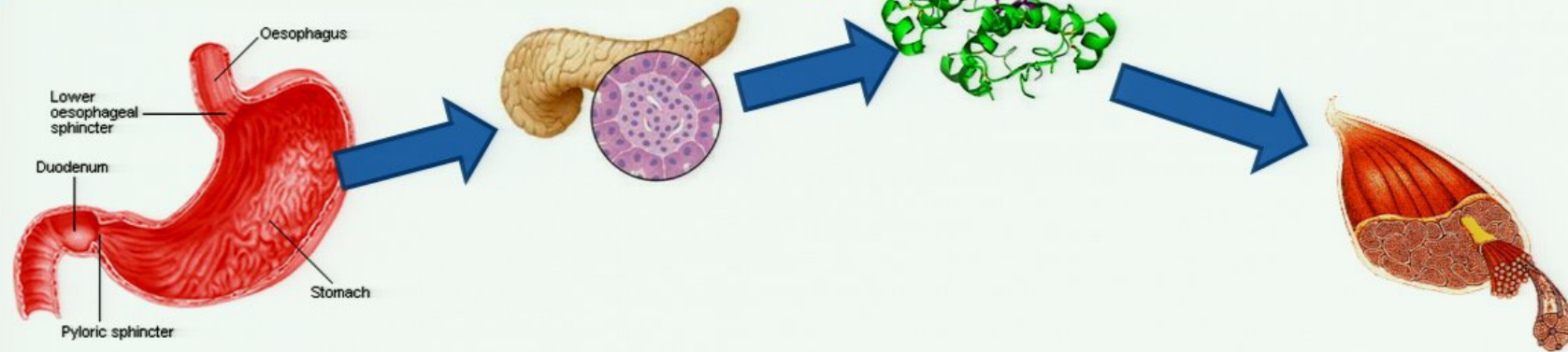
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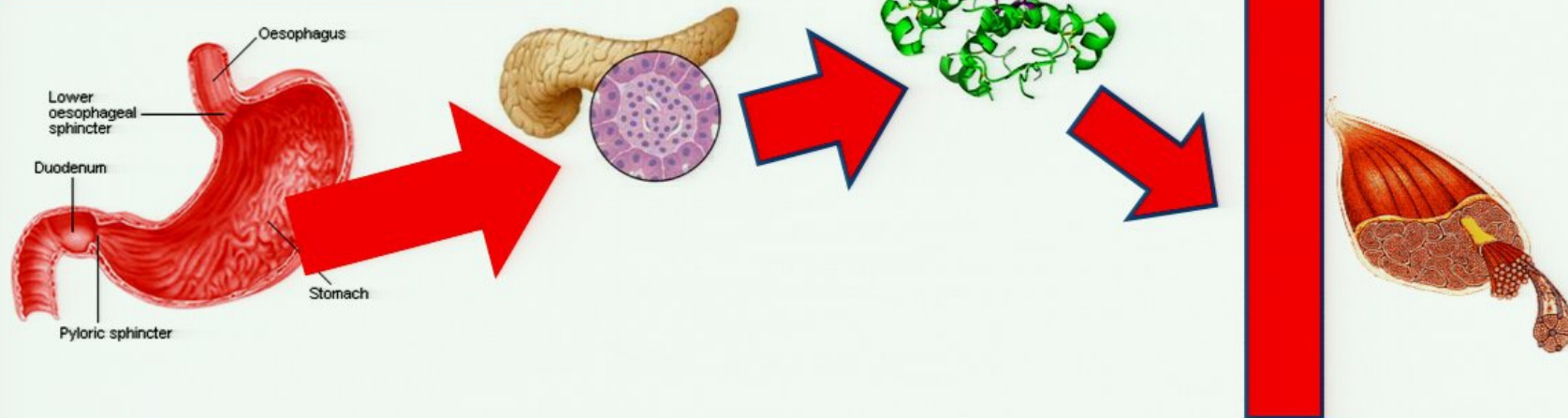
***Proposed view: Hyperglycemia
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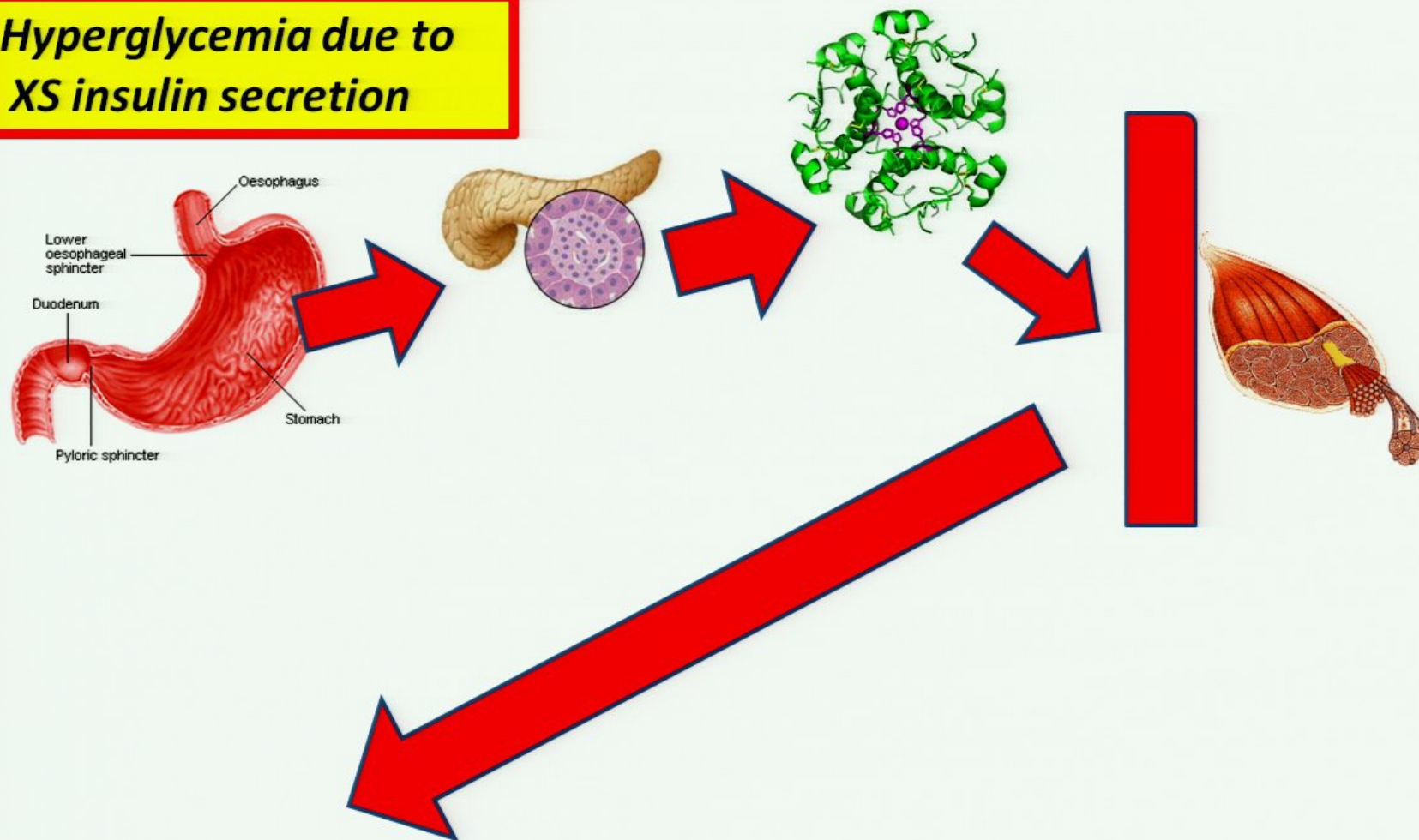
***Proposed view: Hyperglycemia
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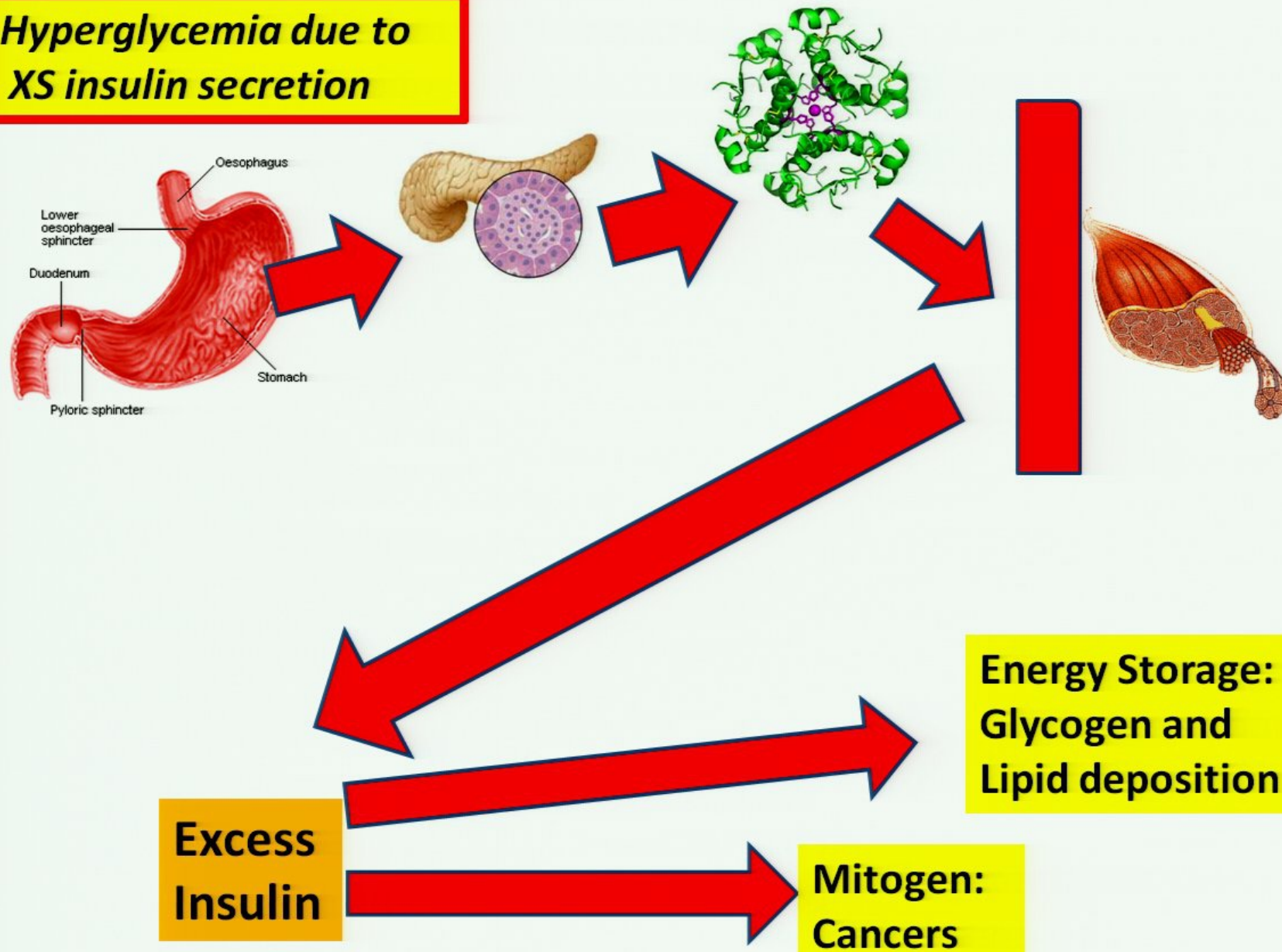
Hyperglycemia due to XS insulin secretion



Hyperglycemia due to XS insulin secretion



Hyperglycemia due to XS insulin secretion



Sorting it out....

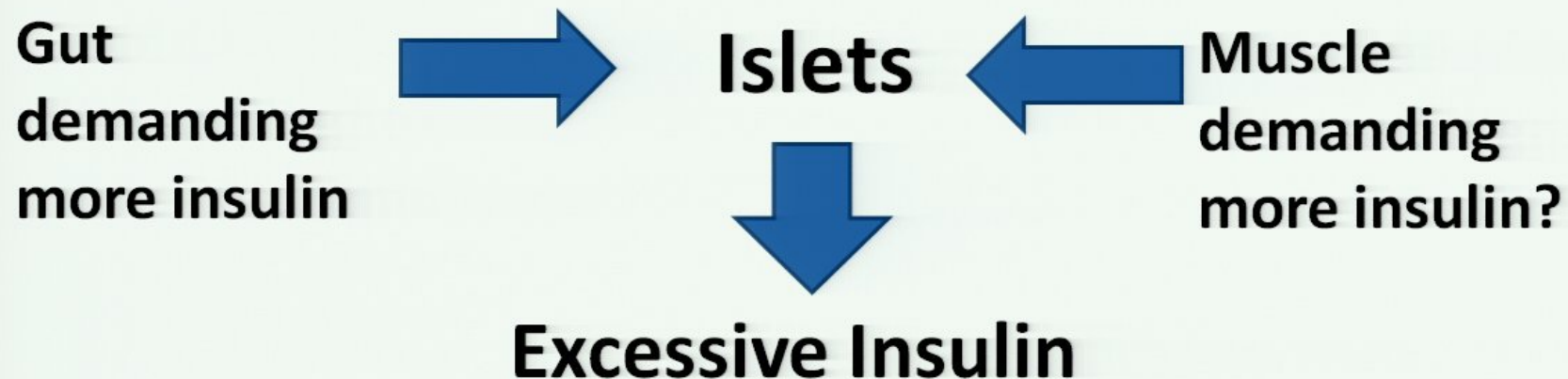
- ***We know the T2DM clears in a matter of days***
- ***Which normalizes at the same speed:***
 - ***Insulin secretion?***
 - ***Insulin resistance?***

The Signal for Hyperinsulinemia

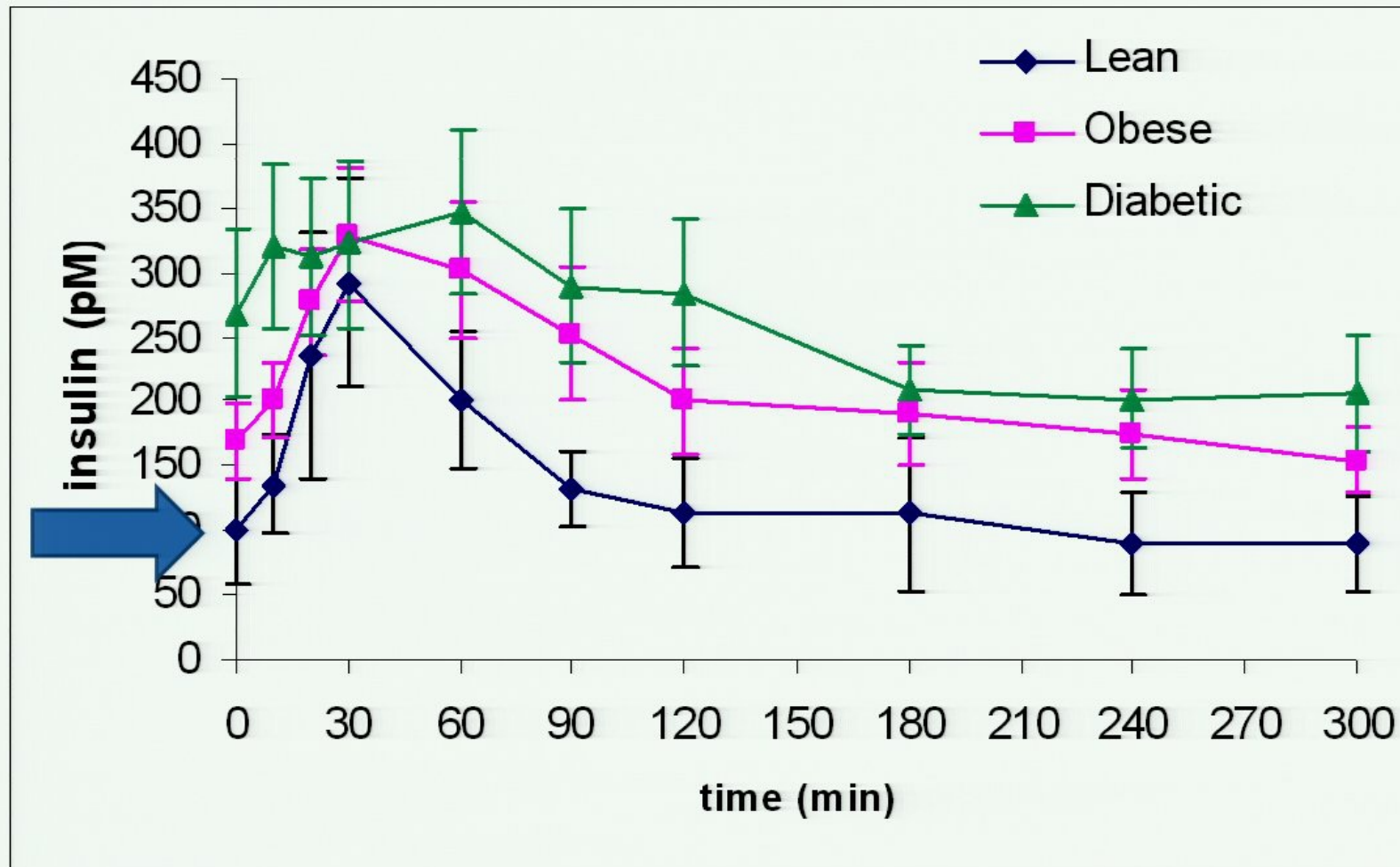
- *Islets are stimulated by the insulin resistance in peripheral tissues to overproduce insulin?*

OR

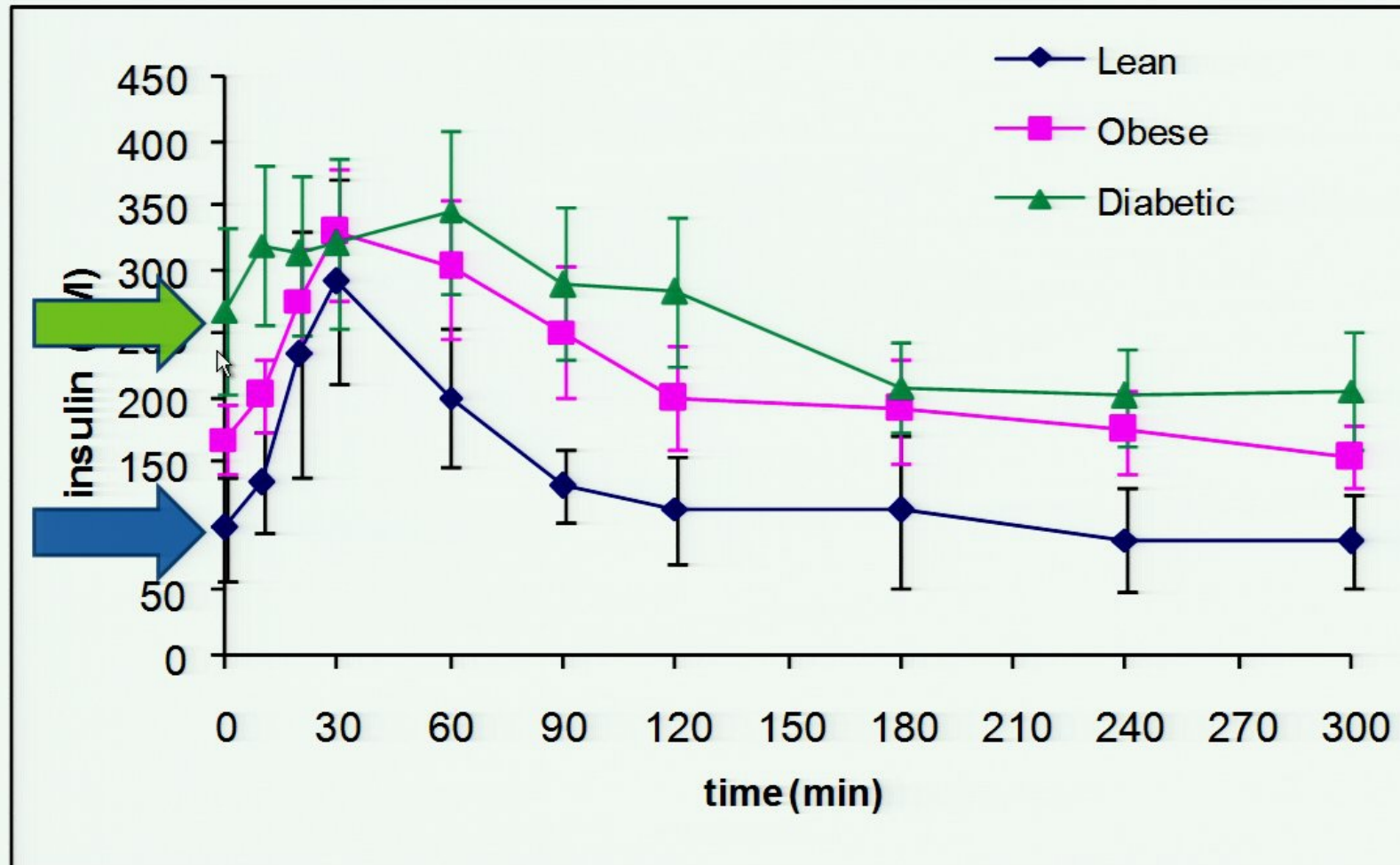
- *Islets are stimulated by abnormal signals from the gut?*



Insulin levels after mid-level caloric meal challenge

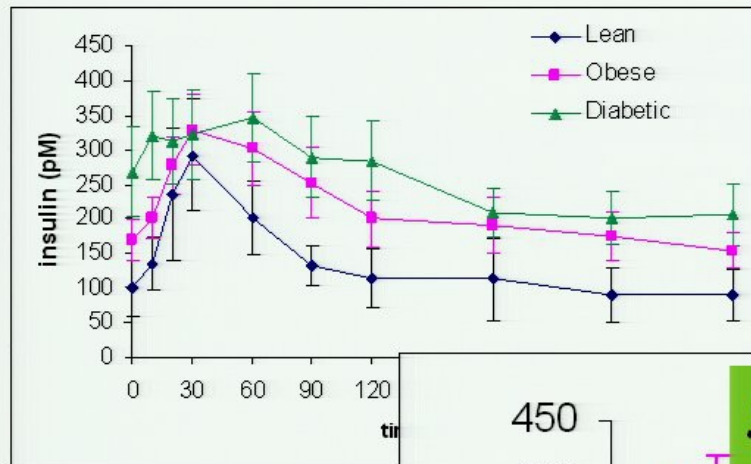


Insulin levels after mid-level caloric meal challenge
Basal insulin level is twice normal; can't respond more



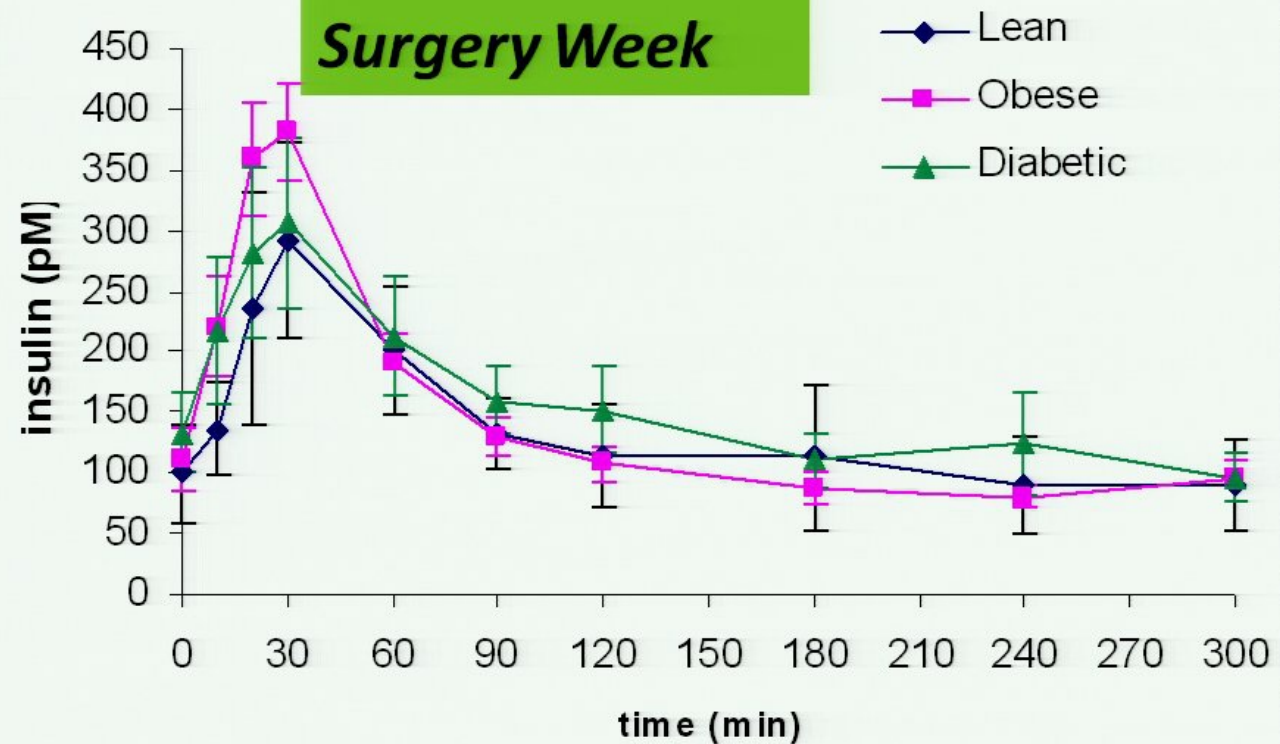
Reed M. submitted 2011

Pre-surgery

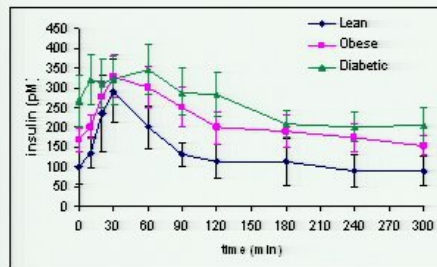


Within a week, the normal insulin levels and response are corrected.....

Surgery Week

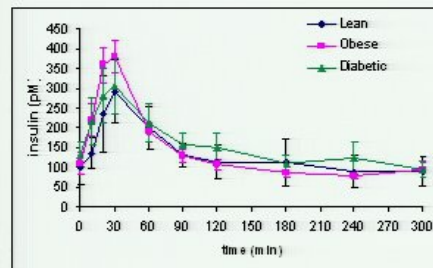


Pre-surgery

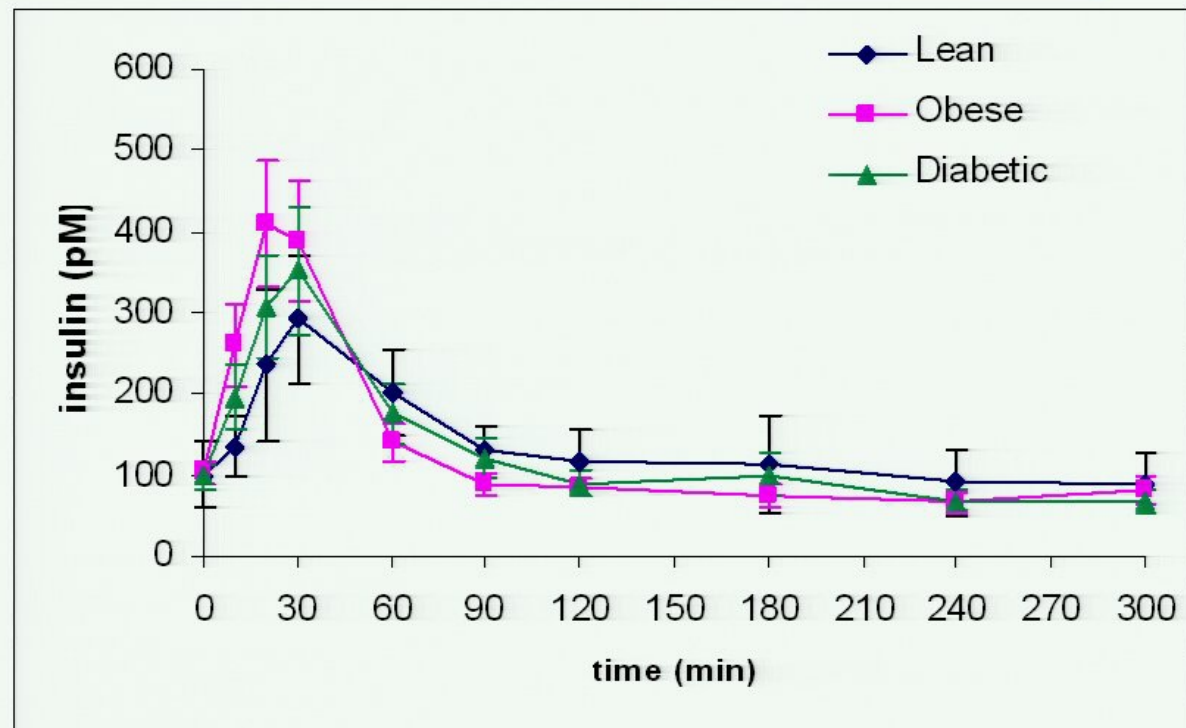


And stay corrected.....

Surgery Week



3 Months Post Surgery



***What can we measure to identify the lesion in
T2DM:***

- 1) Peripheral Resistance***
 - 2) Excessive Insulin Secretion?***
- Which comes first?***

***What can we measure to identify the lesion in
T2DM:***

1) Peripheral Resistance

2) Excessive Insulin Secretion?

Which comes first?

- ***Insulin Sensitivity: Minimal Model***

***What can we measure to identify the lesion in
T2DM:***

1) Peripheral Resistance

2) Excessive Insulin Secretion?

Which comes first?

- ***Insulin Sensitivity: Minimal Model***
- ***Insulin secretion: Minimal Model (AIRg),
Meal test (glucose sensitivity)***
- ***Glucose disposal (AUG for glucose after a
meal)***

***What can we measure to identify the lesion in
T2DM:***

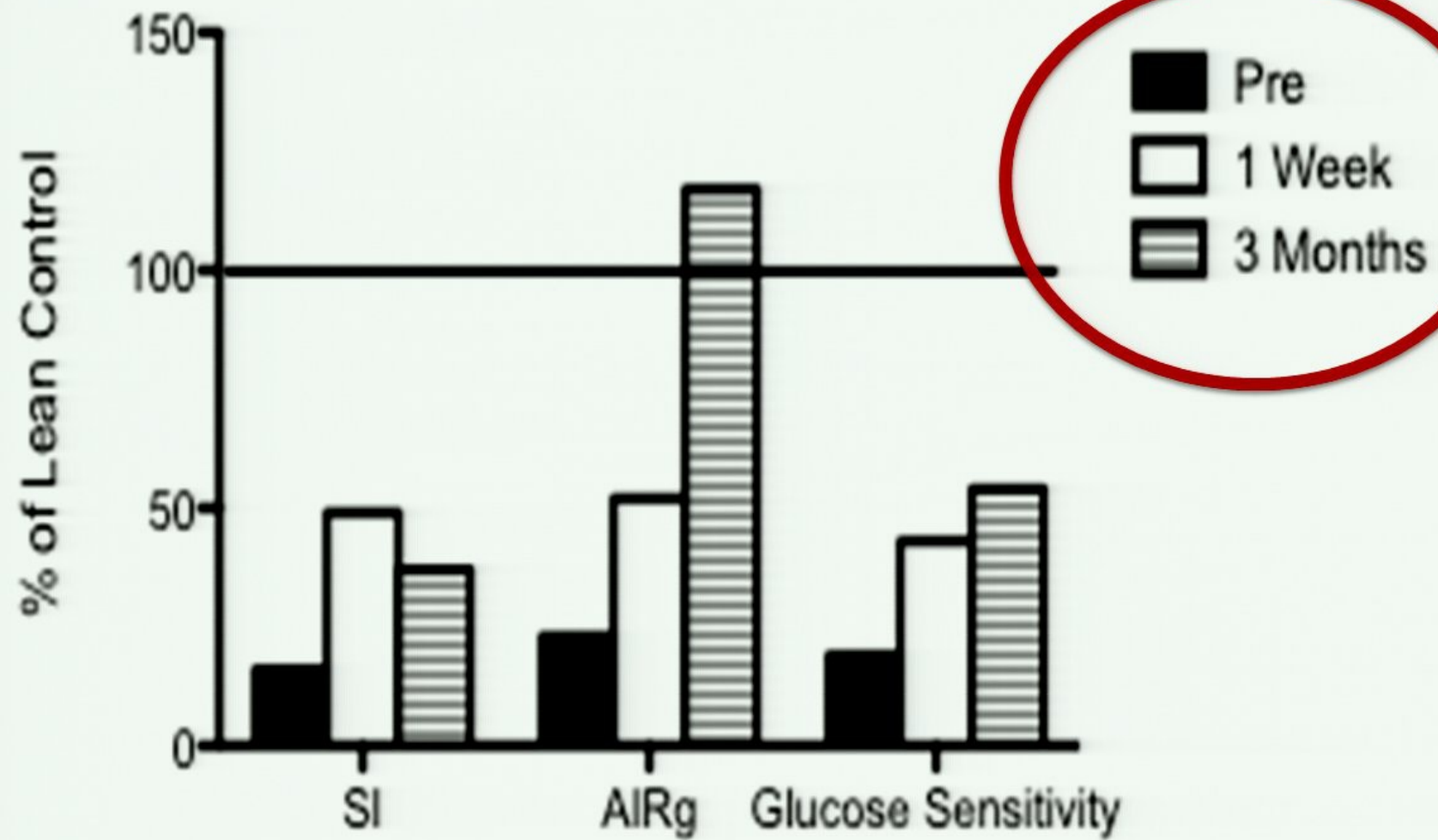
1) Peripheral Resistance

2) Excessive Insulin Secretion?

Which comes first?

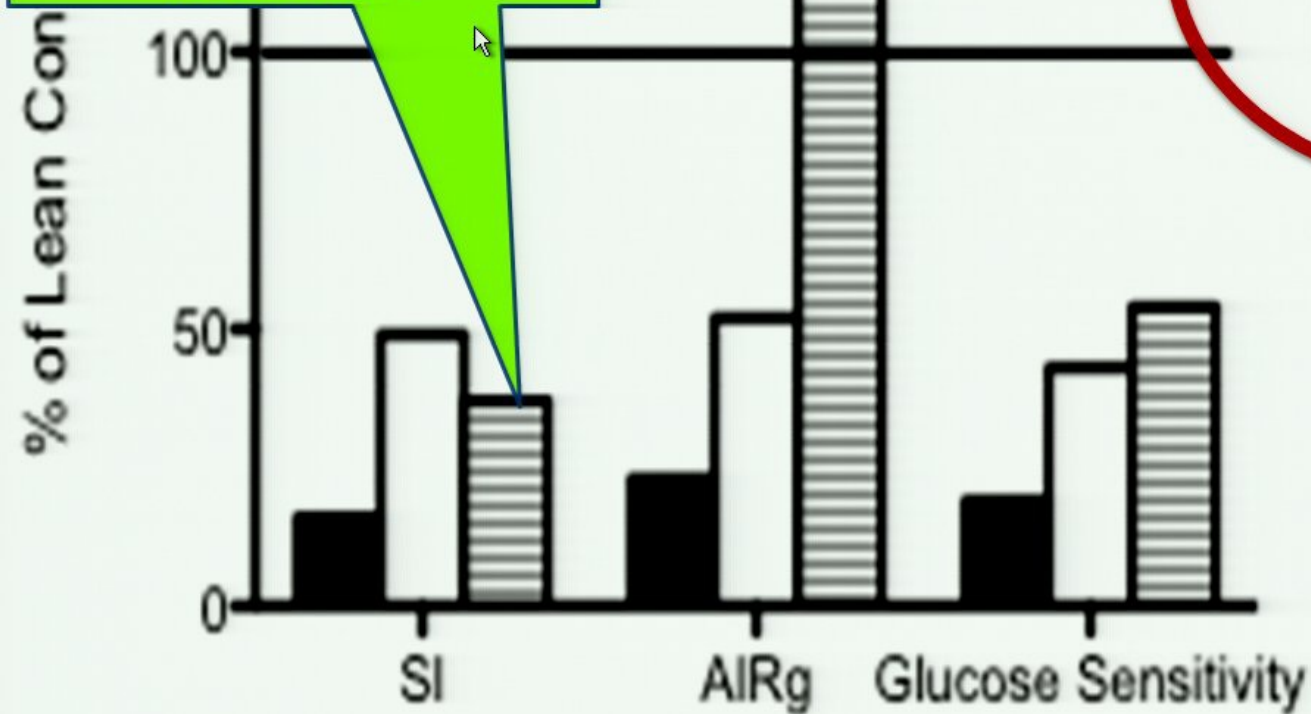
- ***Insulin Sensitivity: Minimal Model***
- ***Insulin secretion: Minimal Model (AIRg),
Meal test (glucose sensitivity)***
- ***Glucose disposal (AUG for glucose after a
meal)***
- ***Glucose production (fasting glucose)***

Insulin Sensitivity and secretion in Type 2 Diabetic patients



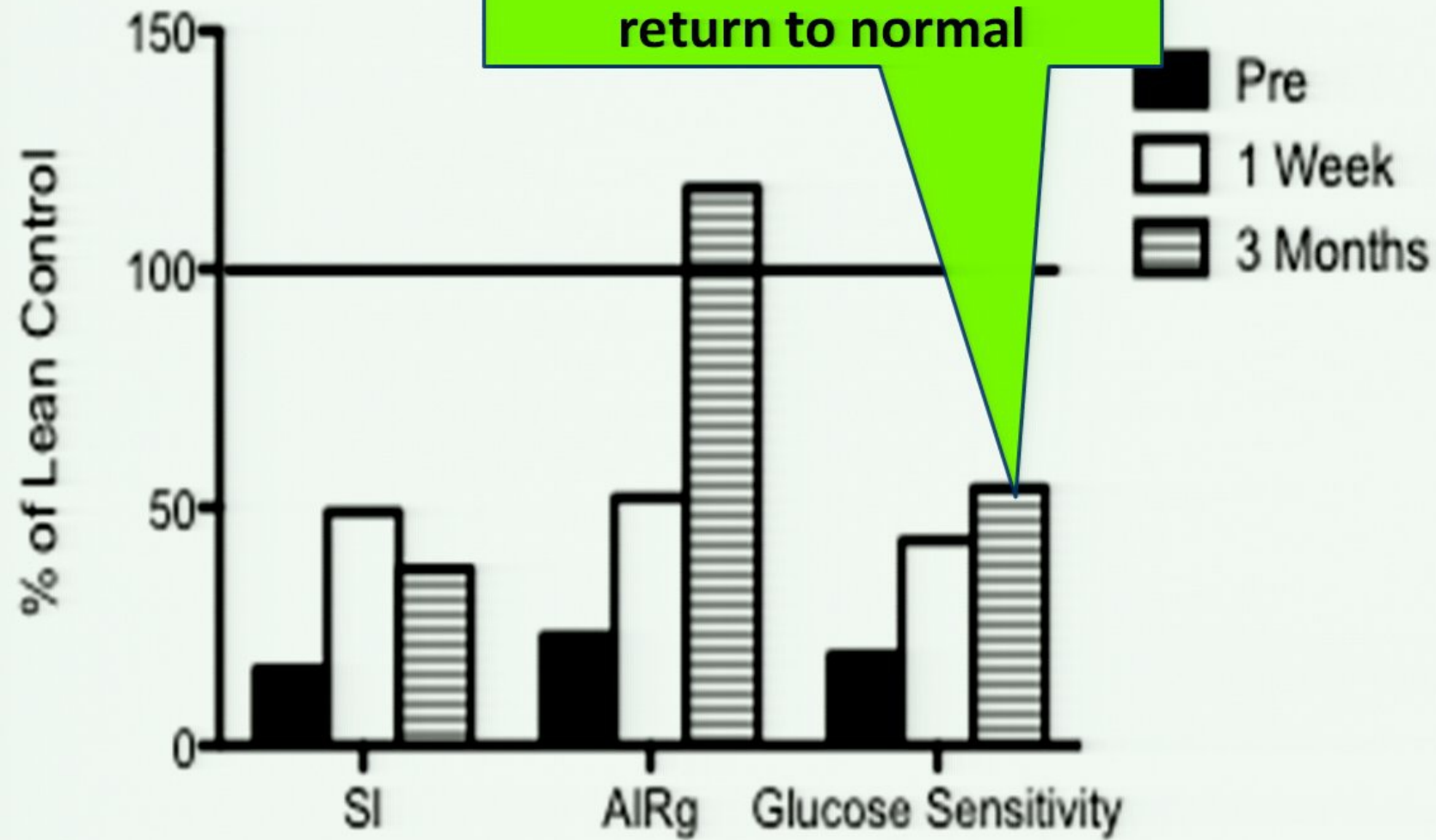
Insulin Sensitivity and secretion in 2 Diabetic patients

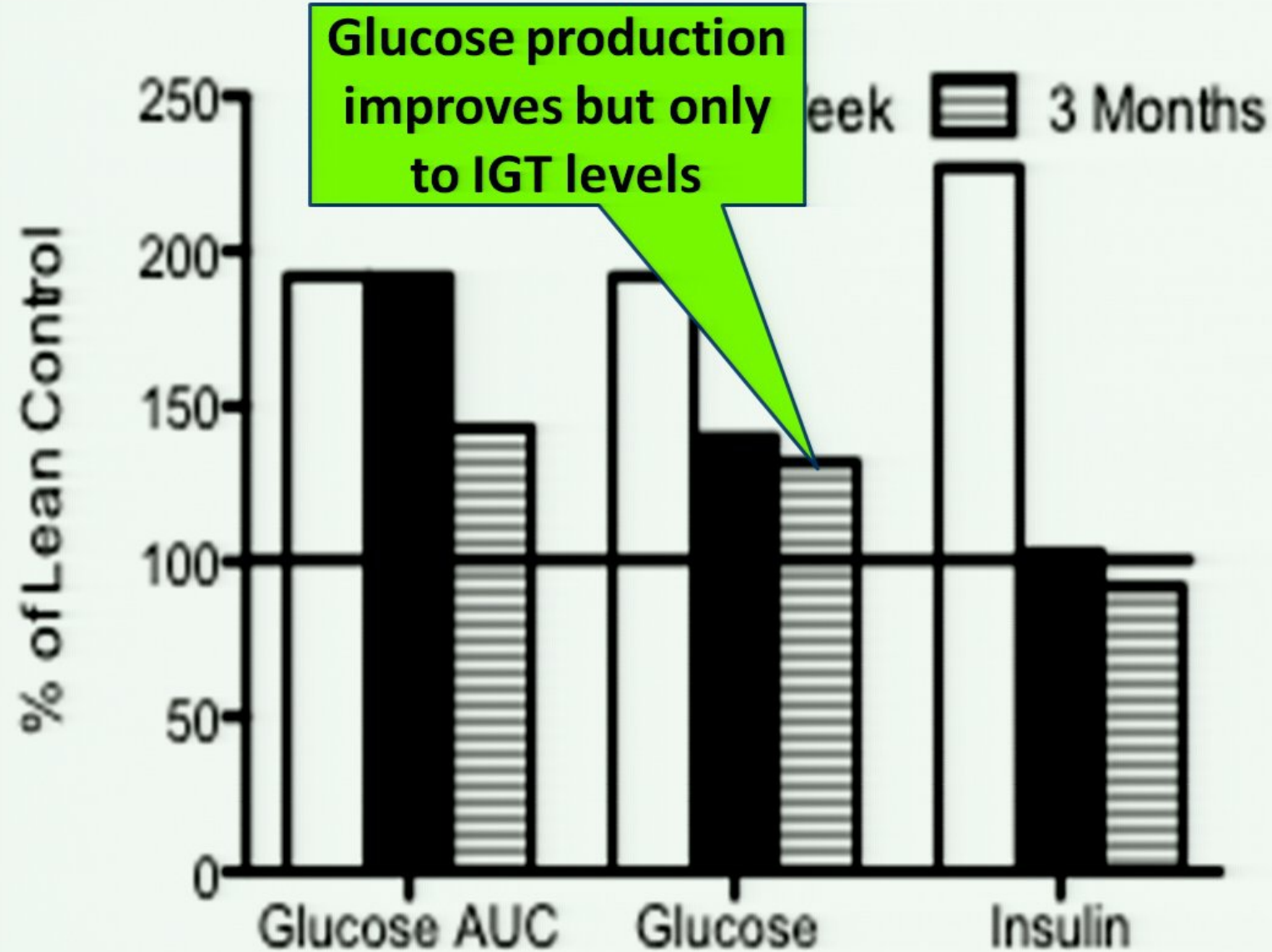
Insulin sensitivity
improves at 3 months
but there is still
profound insulin
resistance



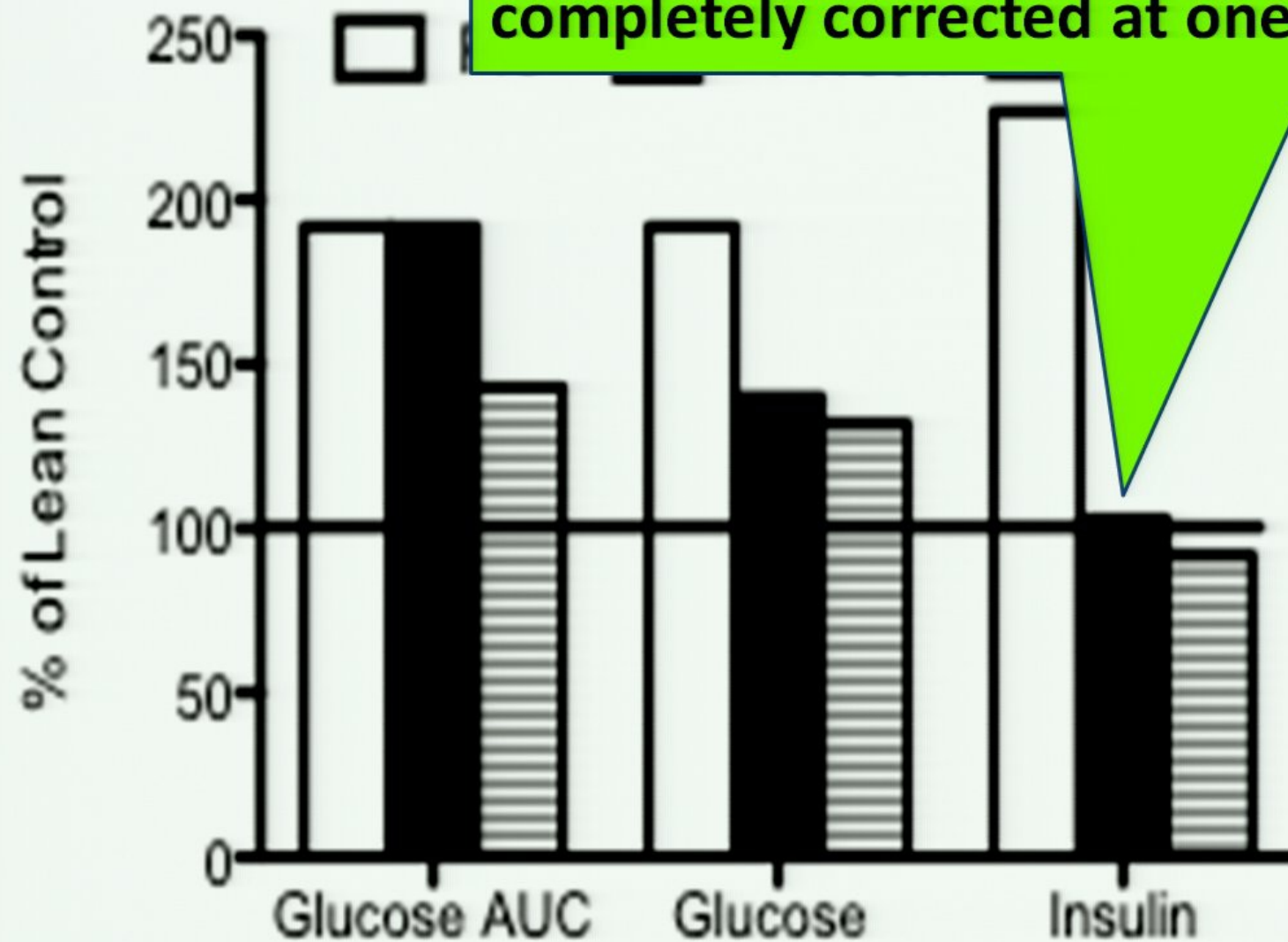
Insulin S
Type

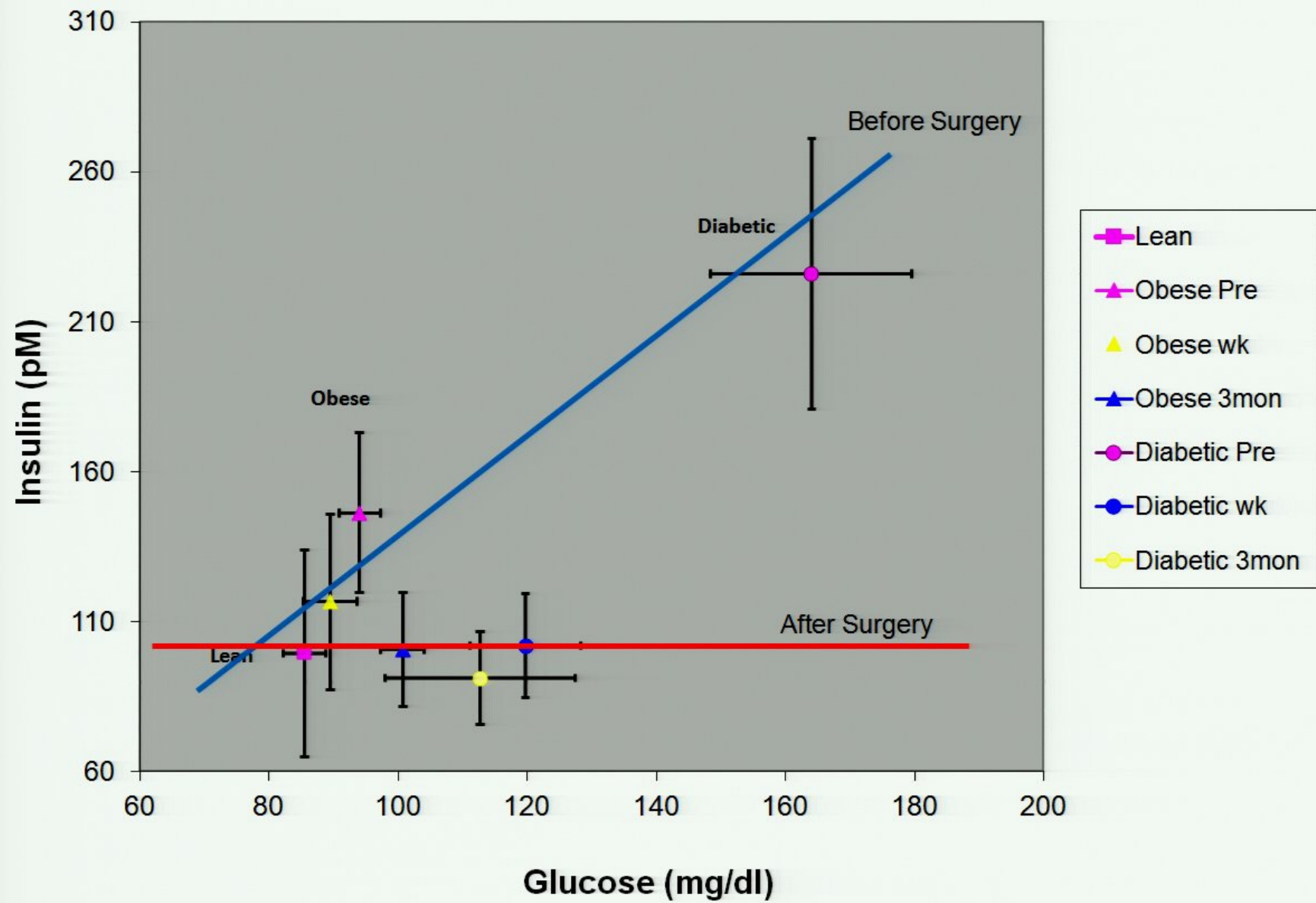
**Glucose sensitivity of
insulin secretion does not
return to normal**





Yet Hyperinsulinemia is completely corrected at one week



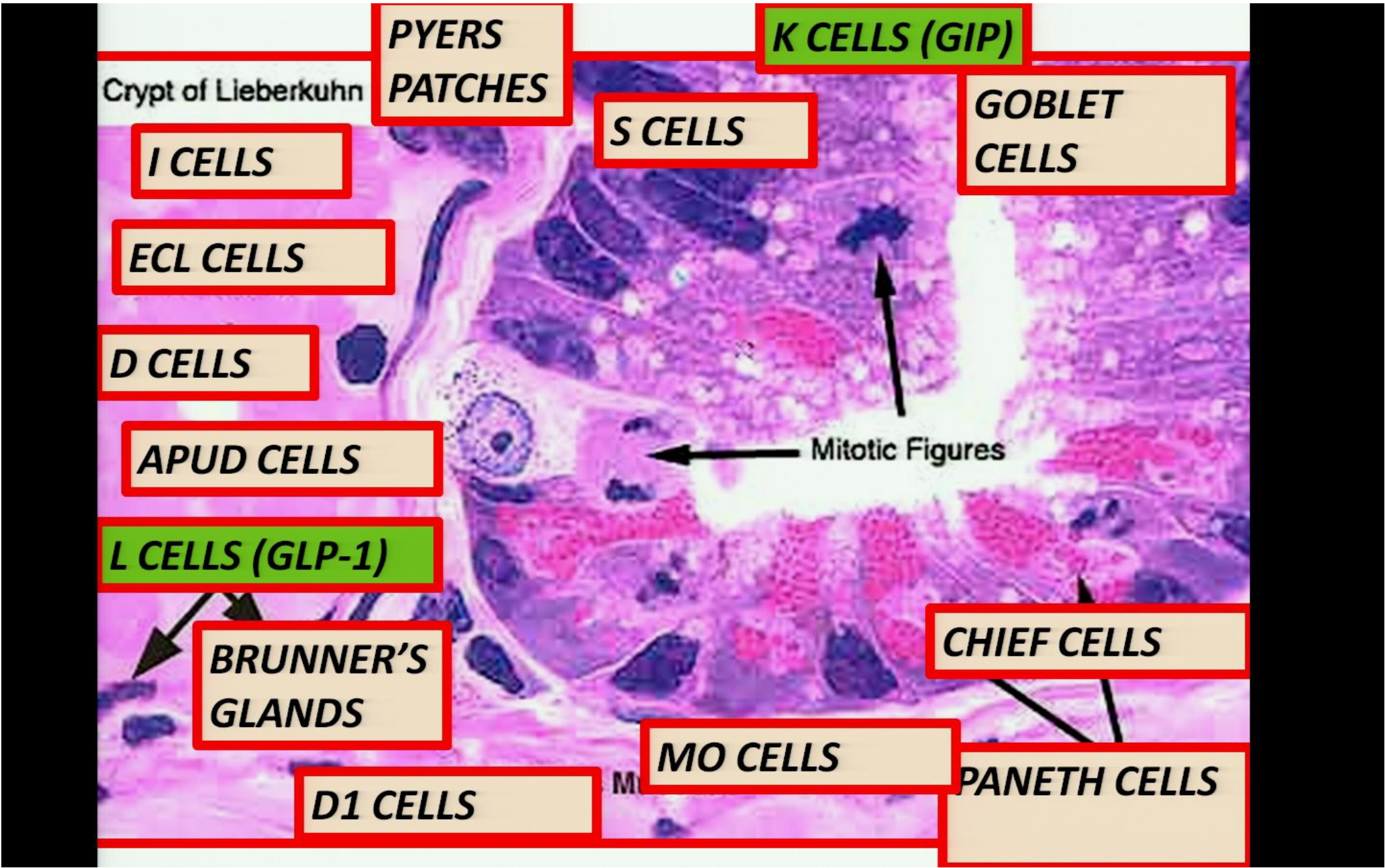


Diabetes clears and Insulin secretion returns to normal even though insulin resistance is still high

Diabetes clears and Insulin secretion returns to normal even though insulin resistance is still high

Conclusion #9: Therefore, most likely, T2DM is caused by abnormal signaling from the gut

Where is the source of the gut signal?



**PYERS
PATCHES**

K CELLS (GIP)

Crypt of Lieberkuhn

I CELLS

S CELLS

**GOBLET
CELLS**

ECL CELLS

D CELLS

APUD CELLS

L CELLS (GLP-1)

*The gut has many
neuroendocrine cells
sending regulatory
signals*

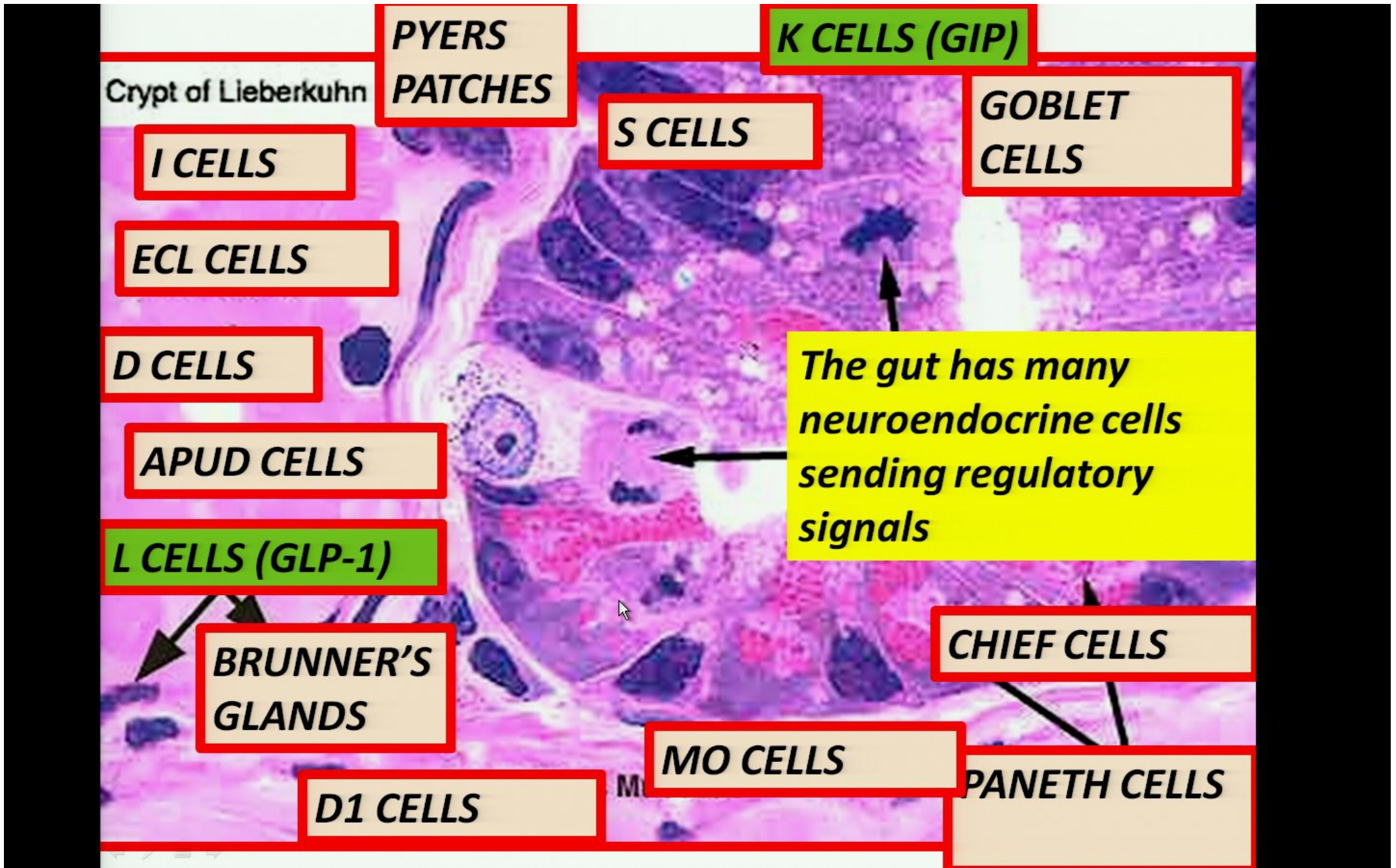
**BRUNNER'S
GLANDS**

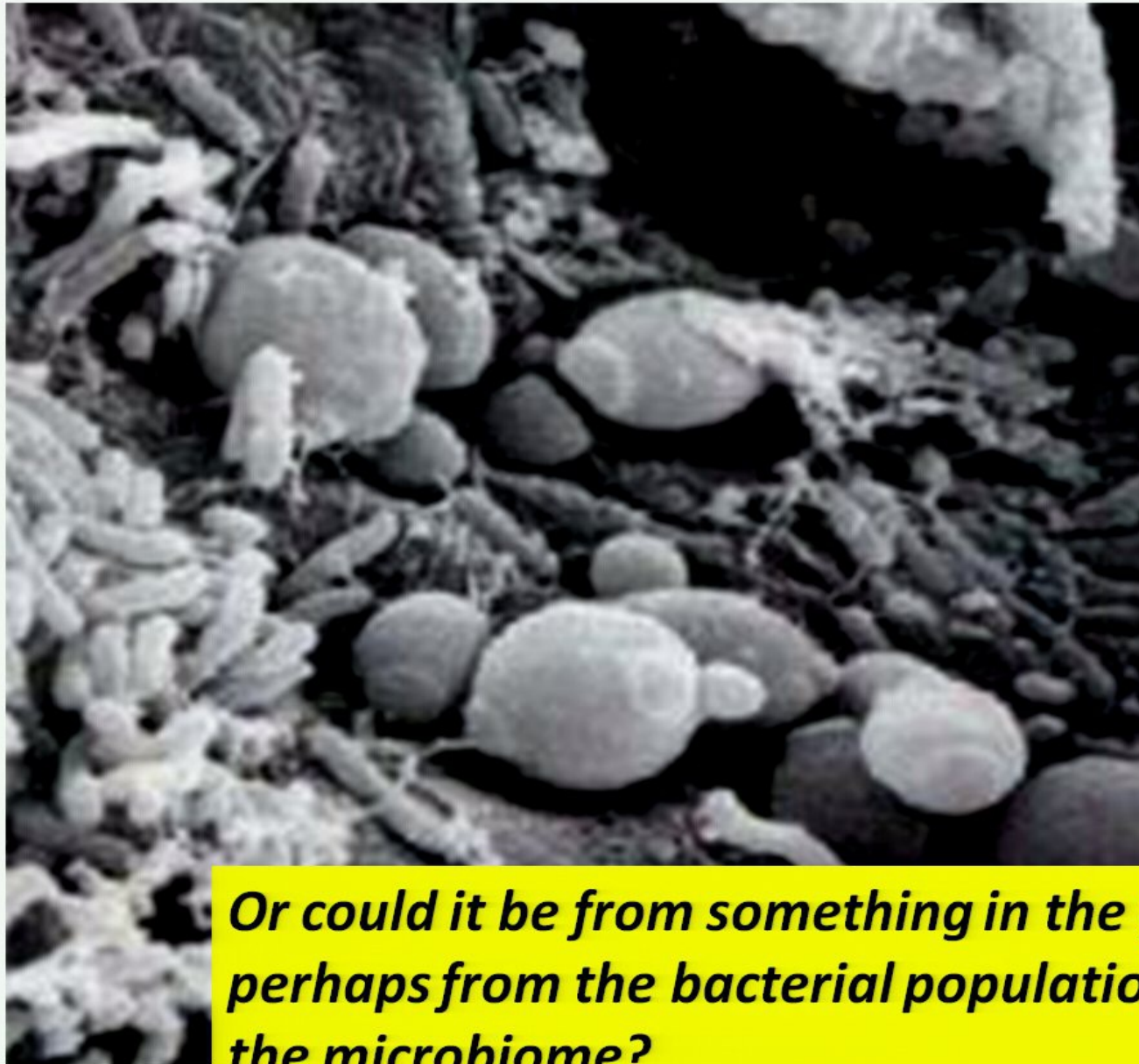
CHIEF CELLS

MO CELLS

PANETH CELLS

D1 CELLS





*Or could it be from something in the gut,
perhaps from the bacterial population,
the microbiome?*

So, if it is true that....

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- ***T2DM patients are hyperinsulinemic and***

So, if it is true that....

- ***T2DM patients are hyperinsulinemic and***
- ***Excess insulin produces fat deposition and atherosclerosis and***

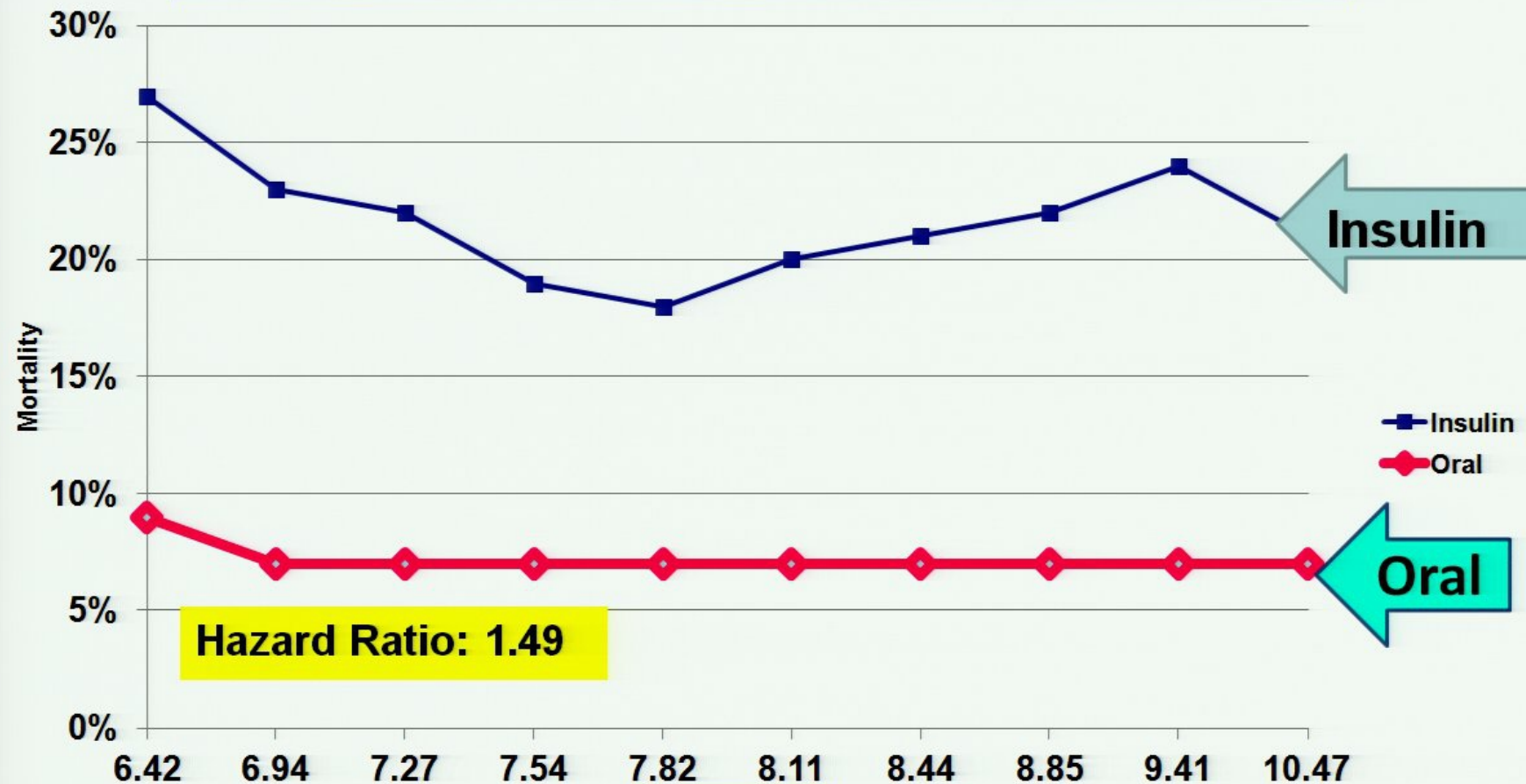
So, if it is true that....

- ***T2DM patients are hyperinsulinemic and***
- ***Excess insulin produces fat deposition and atherosclerosis and***
- ***Excess insulin is a hormone that stimulates cancer***

So, if it is true that....

- *T2DM patients are hyperinsulinemic and*
- *Excess insulin produces fat deposition and atherosclerosis and*
- *Excess insulin is a hormone that stimulates cancer*
- *Should we be treating T2DM patients with insulin?*

Mortality Rates in patients who progressed from oral monotherapy either to 1) multiple oral agents or 2) therapy that included insulin (n= 27,965 vs. 20,005)



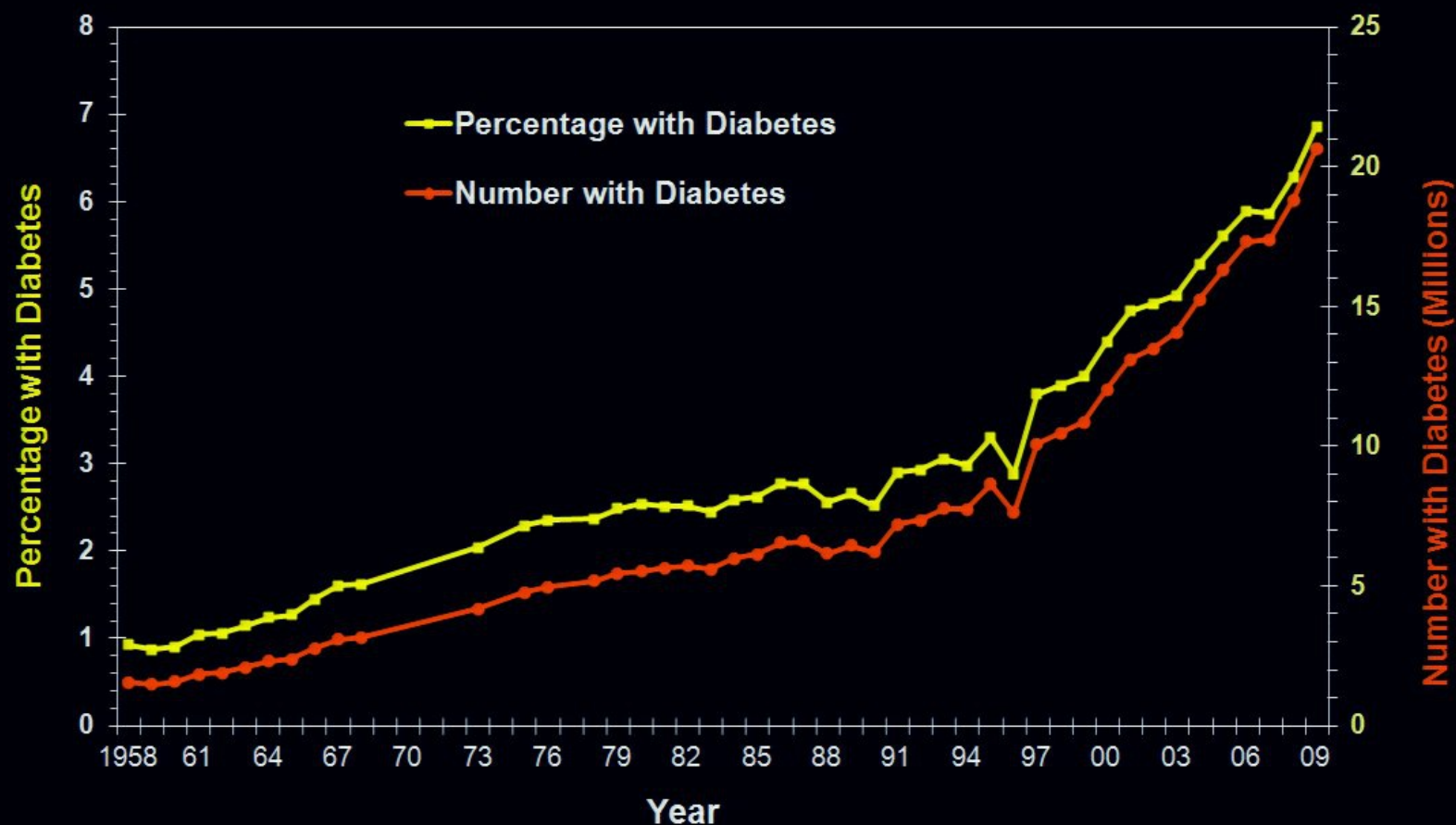
Hazard Ratio: 1.49

Hb1Ac

Currie et al: Lancet, 1/23/2010

***Any ideas about the sudden
increase in T2DM and the
Metabolic Syndrome?***

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2009



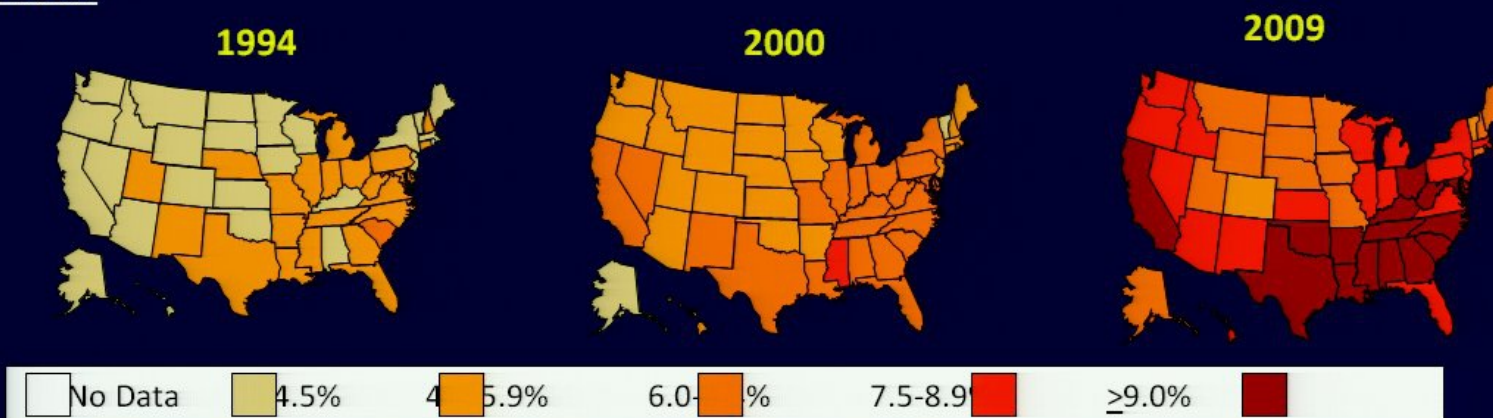
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>

Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

Obesity (BMI ≥ 30 kg/m²)



Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>



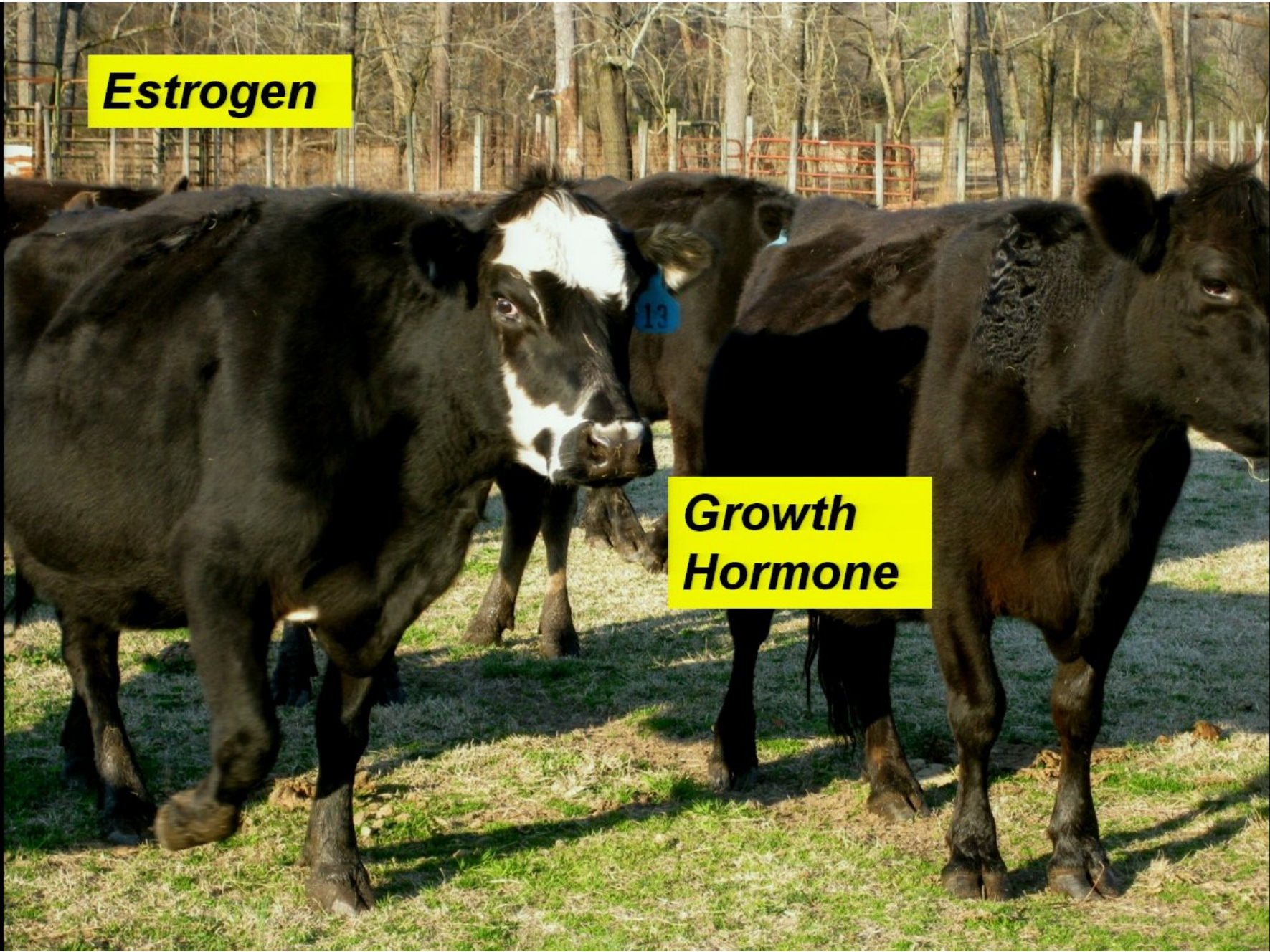


Estrogen



Estrogen

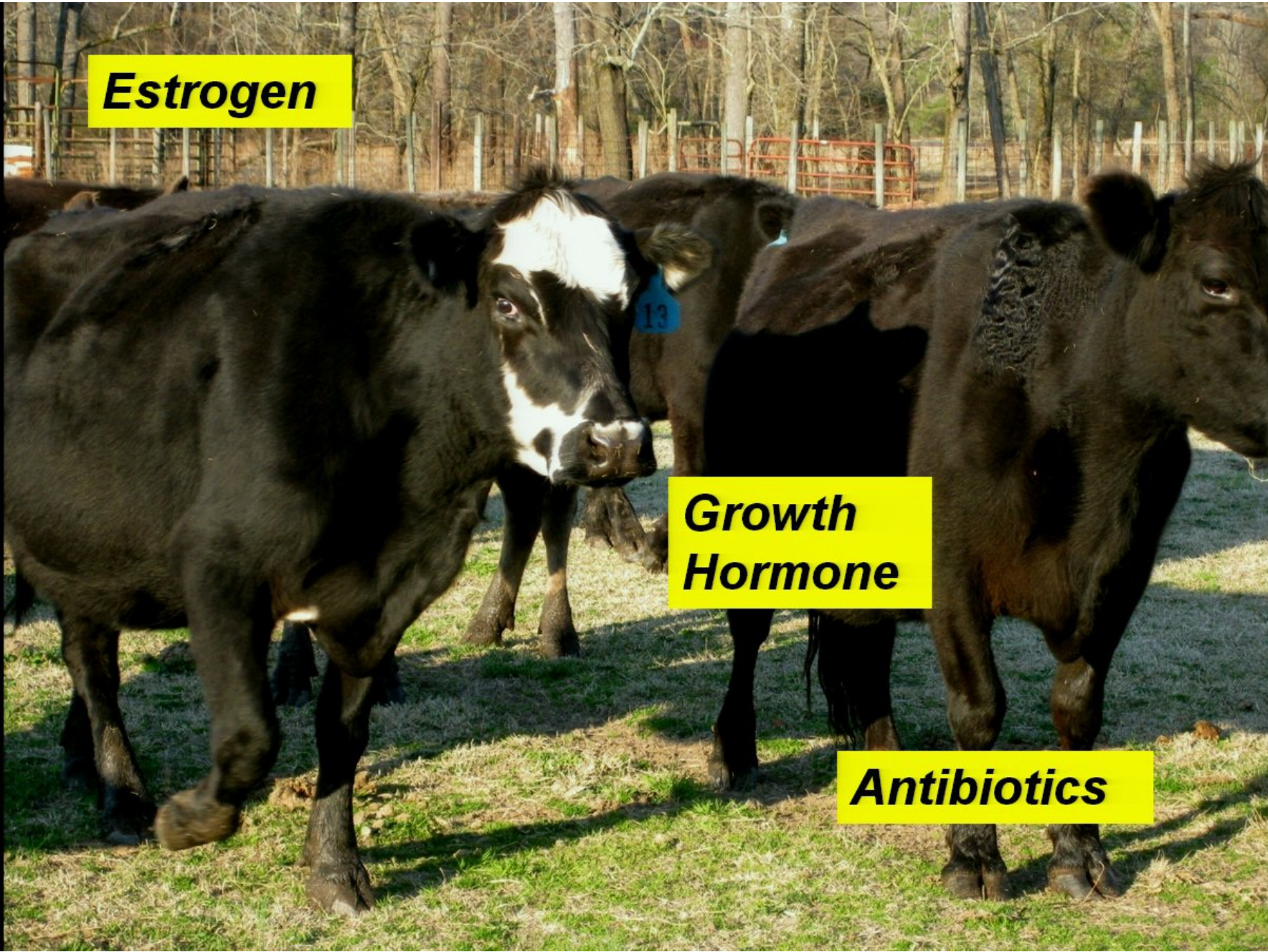
**Growth
Hormone**



Estrogen

***Growth
Hormone***

Antibiotics

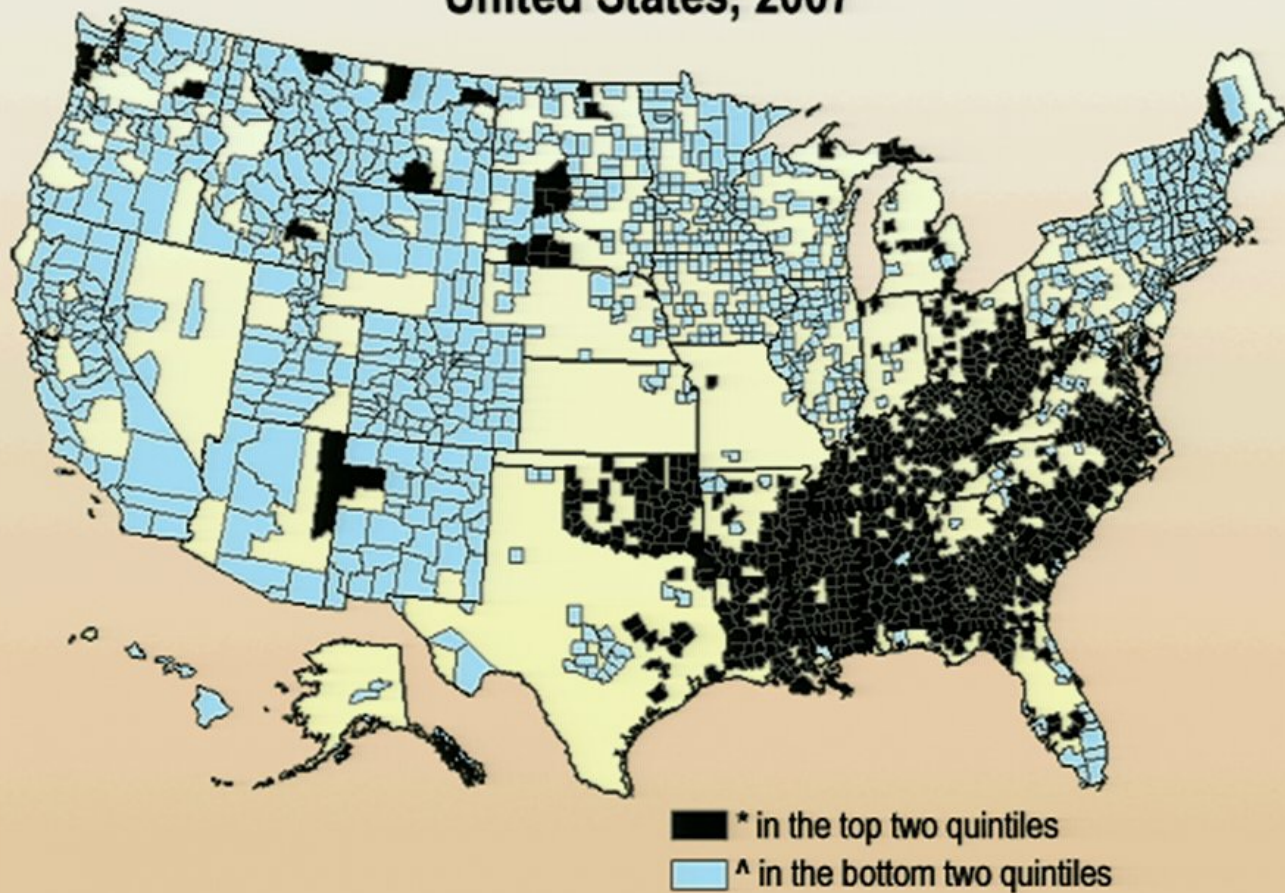




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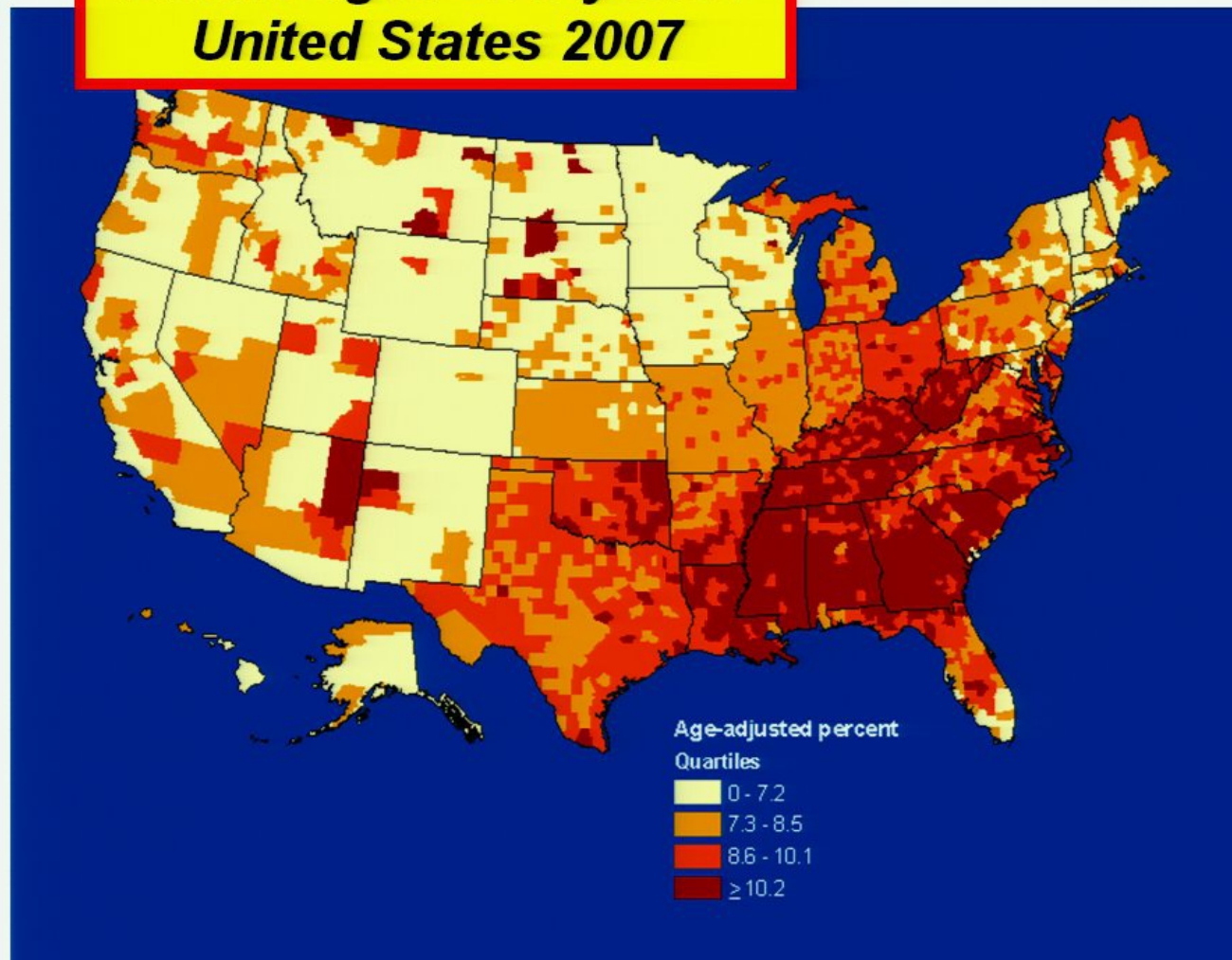


**Diabetes and obesity, by county (in persons aged ≥ 20 years)
United States, 2007**



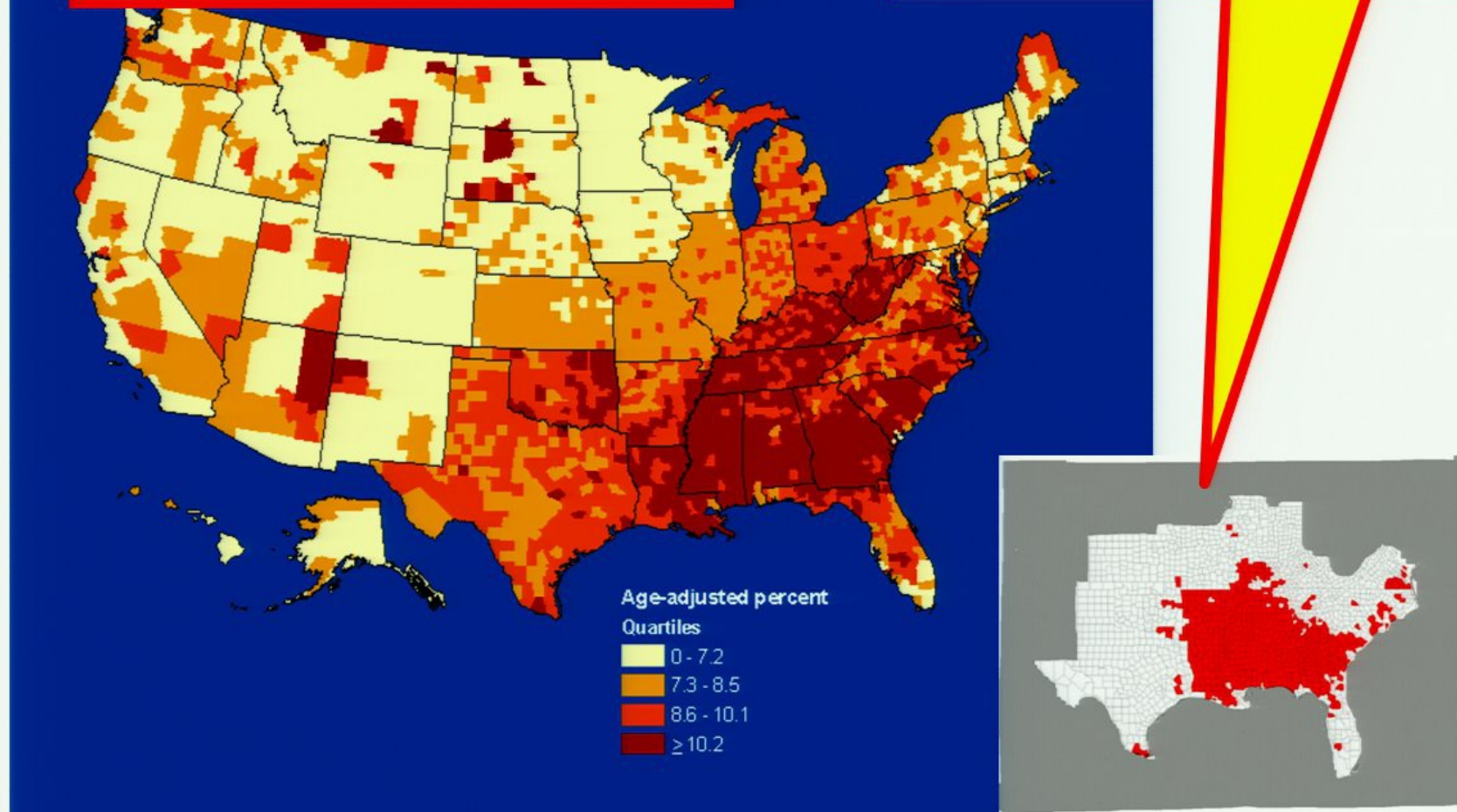
Estimated County-Level Prevalence of Diabetes and Obesity -- United States, 2007. MMWR 58(45):1259-1263.

***Diagnosed Diabetes for
Adults aged ≥ 20 years:
United States 2007***



***Diagnosed Diabetes for
Adults aged ≥ 20 years:
United States 2007***

***2009: Soy Bean Rust
Rx: Fungicides 3 – 5
gallons per acre***



Conclusions

- ***Severe obesity is no longer a hopeless disease***

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- *All can be reversed with bypass of the intestine*
- *These diseases are probably due to an aberrant signal from the gut*
- *We need to find that signal....*
- *And we will*

Research is a Team Sport

G. Lynis Dohm

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Joe Houmard

Bob Tanenberg

Rita Bowden

W. Randolph Chitwood

Michael Rotondo

Paul Cunningham

Jose Caro

Darrell Neufer

Mel Swanson

Moahad Dar





1503:
Leonardo DaVinci



1504: Michaelangelo

