Diabetes Update 2009

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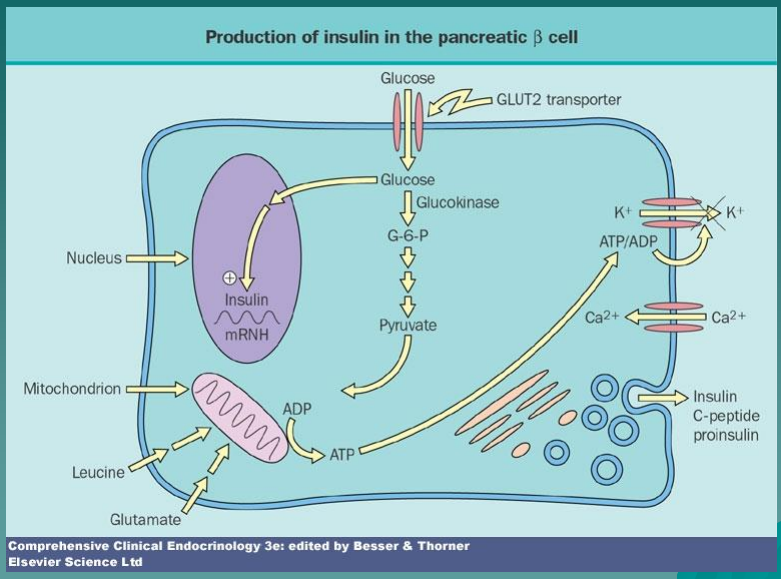
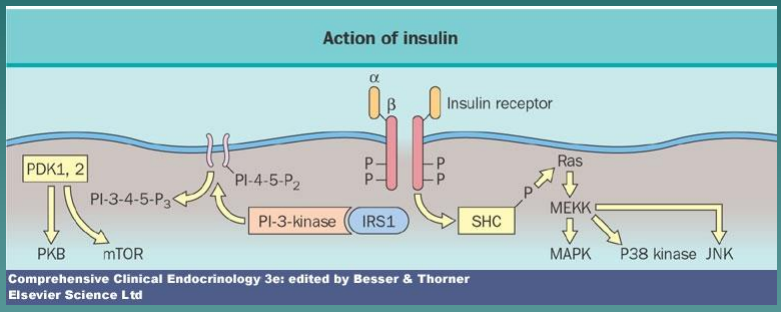
Endocrine and Diabetes Clinic

Objectives

- Review normal glucose metabolism
- Discuss pathophysiology of diabetes mellitis, type 2
- Review types of pharmacotherapy used to treat DM-2
- New treatment modalities
- Prevention strategies


Production of insulin in the pancreatic β cell
Glucose
GLUT2 transporter
Glucose
Glucokinase
G-6-P
Pyruvate
Nucleus
Insulin
mRNH
Mitochondrion
ADP
ATP
Leucine
Glutamate
K+
K+
ATP/ADP
Ca2+
Ca2+
Insulin
C-peptide
proinsulin
Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
Elsevier Science Ltd


Action of insulin
α
β
Insulin receptor
PDK1, 2
PI-4-5-P2
PI-3-4-5-P3
PI-3-kinase
IRS1
P
P
P
P
P
SHC
Ras
MEKK
PKB
mTOR
MAPK
P38 kinase
JNK
Comprehensive Clinical Endocrinology 3e: edited by Besser & Thorner
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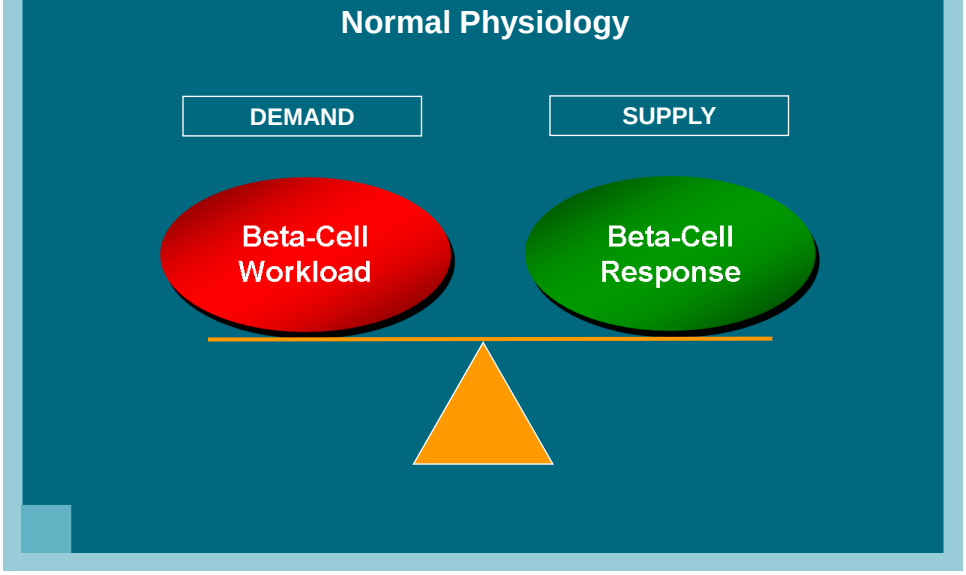
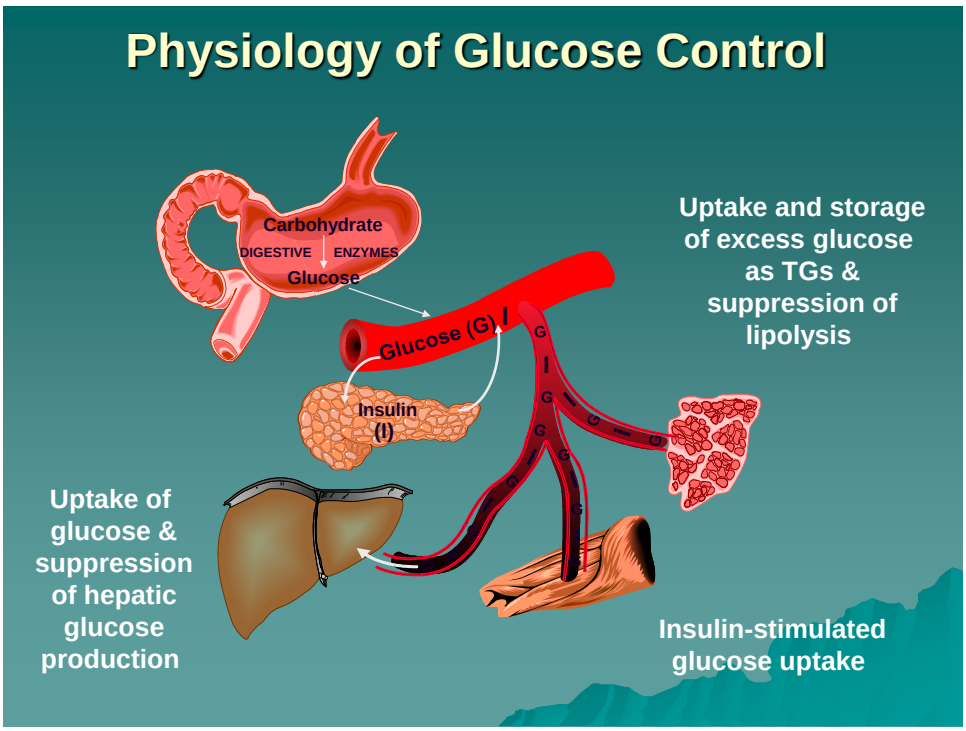
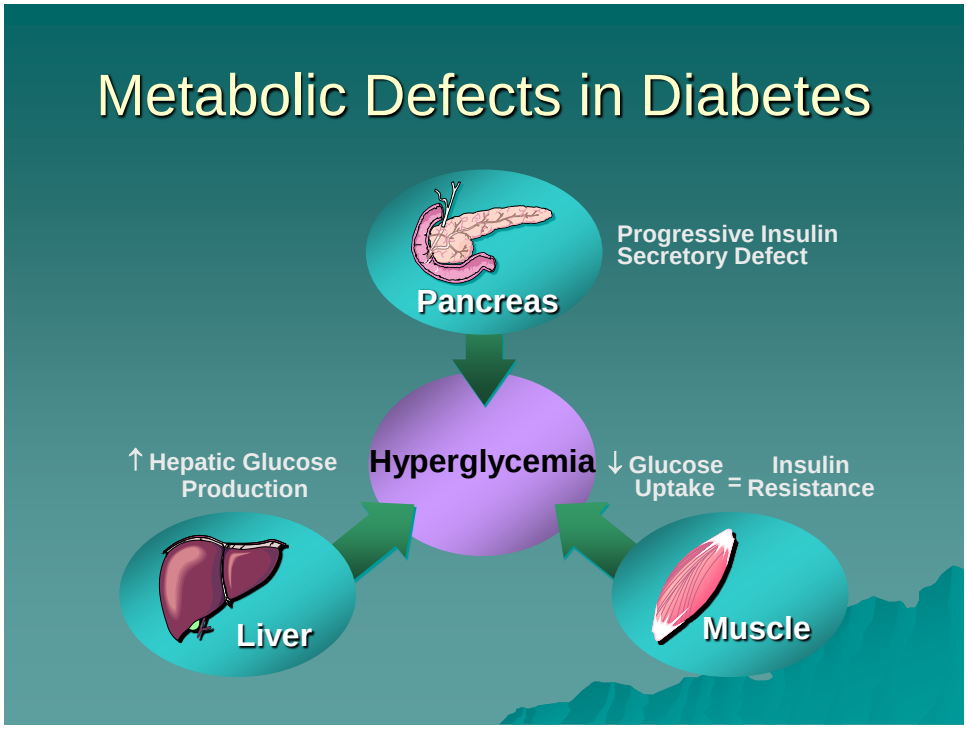
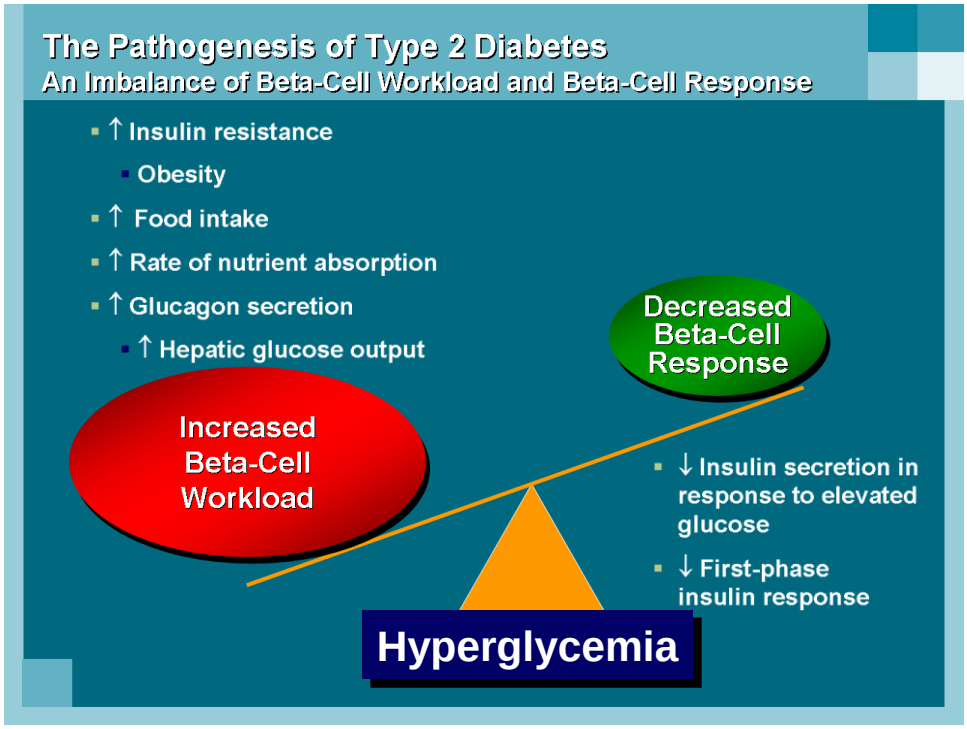
Beta-Cell Workload and Beta-Cell Response
Normally Balanced to Maintain Euglycemia



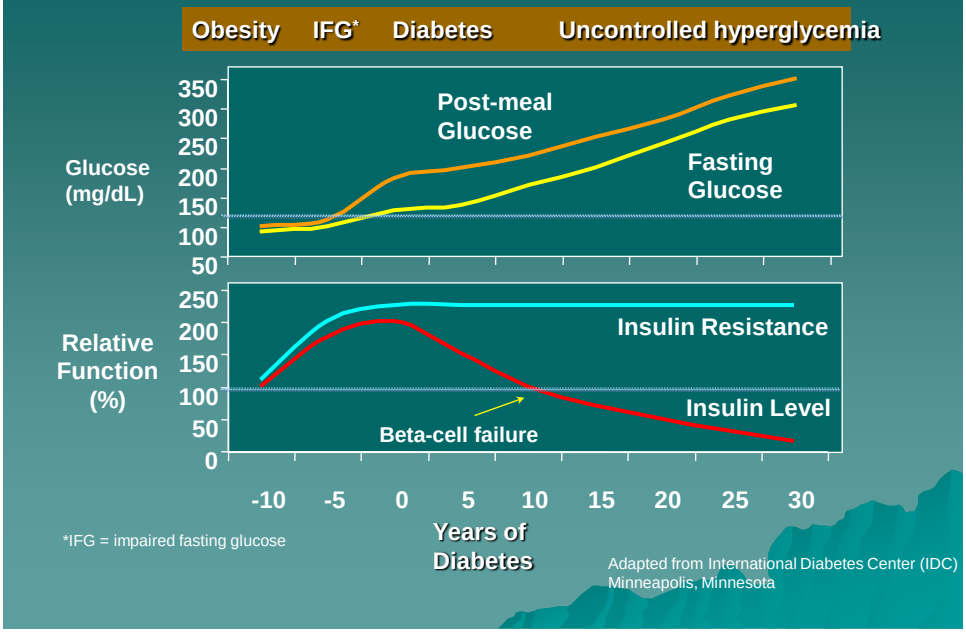
Physiology of Glucose Control




Metabolic Defects in Diabetes
Pancreas
Progressive Insulin Secretory Defect
↑ Hepatic Glucose Production
Hyperglycemia
↓ Glucose Uptake
= Insulin Resistance
Liver
Muscle


The Pathogenesis of Type 2 Diabetes
An Imbalance of Beta-Cell Workload and Beta-Cell Response
↑ Insulin resistance
Obesity
↑ Food intake
↑ Rate of nutrient absorption
↑ Glucagon secretion
↑ Hepatic glucose output
Decreased Beta-Cell Response
Increased Beta-Cell Workload
↓ Insulin secretion in response to elevated glucose
↓ First-phase insulin response
Hyperglycemia

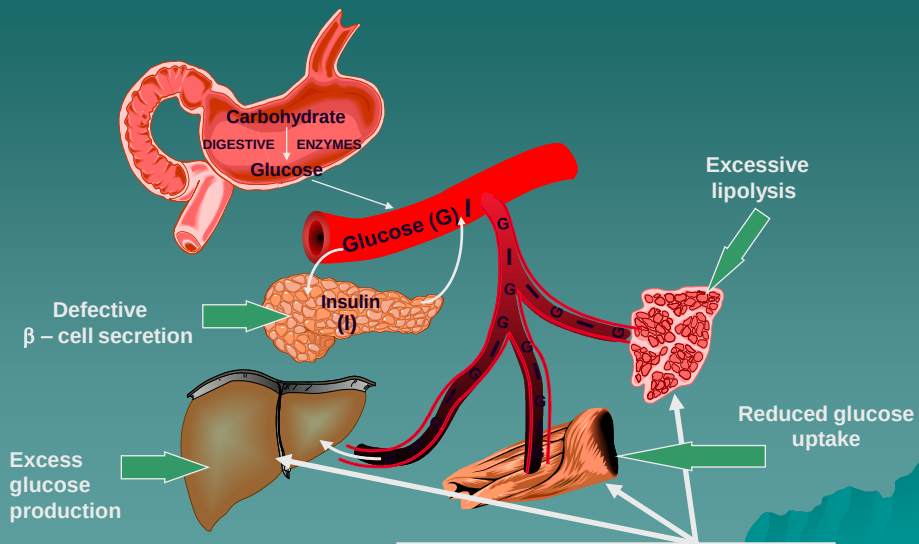
Natural History of Type 2 Diabetes



*IFG = impaired fasting glucose

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota

Pathophysiology of Type 2 Diabetes

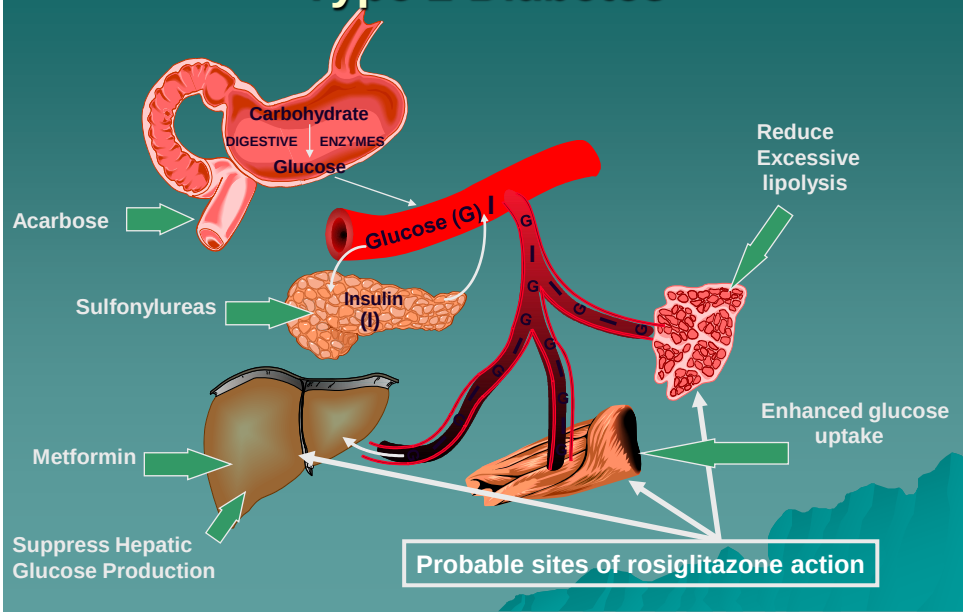


Pharmacologic Classes of Agents to Control Hyperglycemia in DM- 2

Class	Action
Thiazolidinediones—e.g., rosiglitazone, pioglitazone	Bind to peroxisome proliferator activated receptor-gamma (PPARγ) in muscle, fat and liver to decrease insulin resistance
Insulin secretagogues—e.g.,sulfonylureas	Stimulate pancreatic β-cells to increase insulin output
Biguanides—e.g., metformin	Target liver to decrease glucose production
Alpha-glucosidase inhibitors—e.g., acarbose & miglitol	Inhibit intestinal enzymes that break down carbohydrates, which delays carbohydrate absorption
Insulin	Target insulin-sensitive tissue to increase glucose uptake

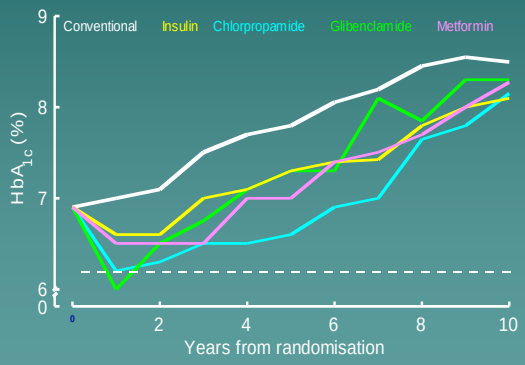
Krenz et al. *Drug Safety*. 1994;11:223-241. Bloomgarden. *Clinical Therapeutics*. 1998;20:216-231. Spiegelman. *Diabetes*. 1998;47:507-514. Saltiel et al. *Diabetes*. 1998;445:1661-1669. American Diabetes Association. Consensus Statement on Pharmacological Treatment. *Diabetes Care*. 1995;18:1510-1518.

Pharmacologic Intervention in Type 2 Diabetes



Current Therapies Do Not Influence Beta-Cell Failure

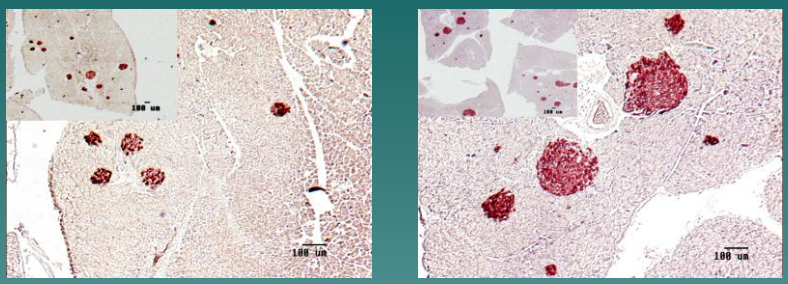
cohort, median data



Source: UKPDS. *Lancet* 1998

- Long-term glycemic control not easily attained or maintained
- Polypharmacy with oral agents with complementary mechanisms may be necessary to achieve long-term control

Rosiglitazone Increases Islet Area and Density in Pancreatic Islets of *db/db* Mice

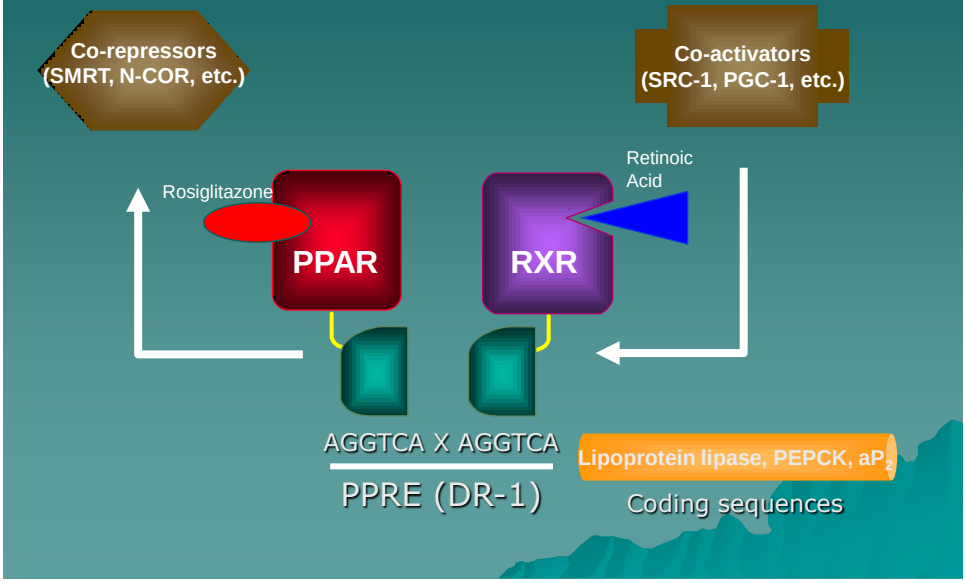


Control **Rosiglitazone**

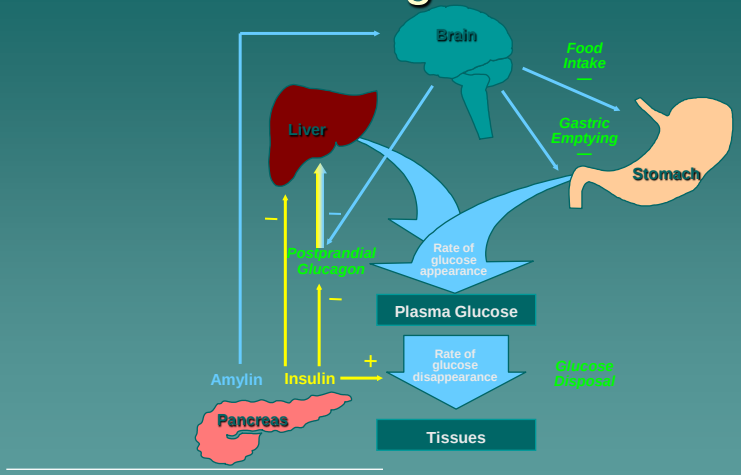
Scale 100 um (enlarged view)

- Improvements in pancreatic islet insulin content and morphology observed in models of type 2 DM

Activation of PPARγ Alters Expression of Specific Genes



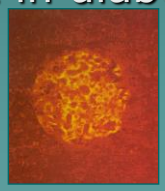
Model of Multihormonal Regulation

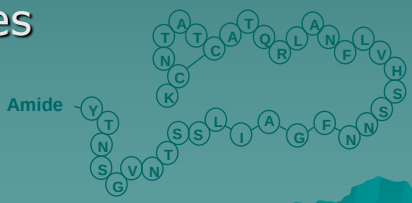


Model derived from animal studies

Amylin the Hormone

- Reported in 1987
- 37-amino acid peptide
- Co-located and co-secreted with insulin from pancreatic β-cells
- Deficient in diabetes





Unger RH, Foster DW. *Williams Textbook of Endocrinology (8th edition)* 1992; 1273-1275
Photographs reprinted with permission of Elsevier

Effect of Amylin on Postprandial Glucose Excursions

- In animal models, amylin has been shown to:
  - Suppress postprandial glucagon secretion
    - glucagon is an important determinant of hepatic glucose production
    - postprandial glucagon is abnormally elevated in diabetes

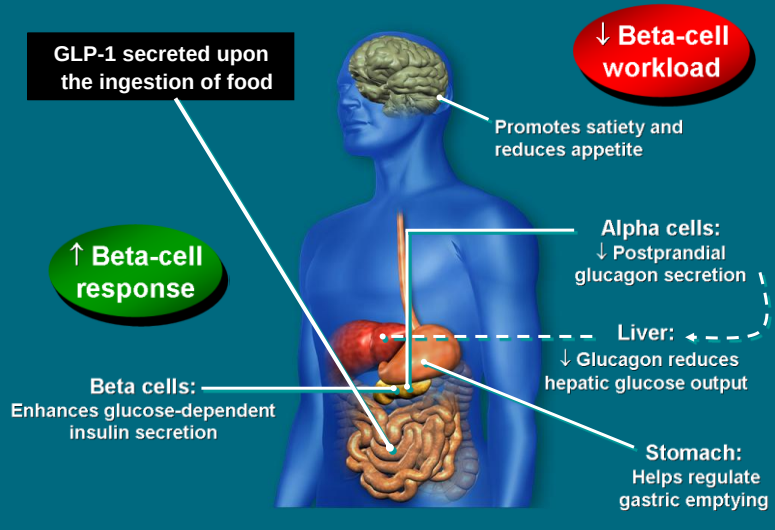
Gedulin B, et al. *Metabolism* 1997; 46:67-70
Young A, et al. *Diabetologia* 1995; 38:642-648
Rushing PA, et al. *Endocrinology* 2000; 141:850-853

Effect of Amylin on Postprandial Glucose Excursions

- Regulate gastric emptying
  - regulates rate of gastric emptying from stomach to small intestine
  - rate of gastric emptying is an important determinant of early glucose excursion postprandially
- Reduce food intake and body weight

GLP-1 Effects in Humans

Understanding the Natural Role of Incretins



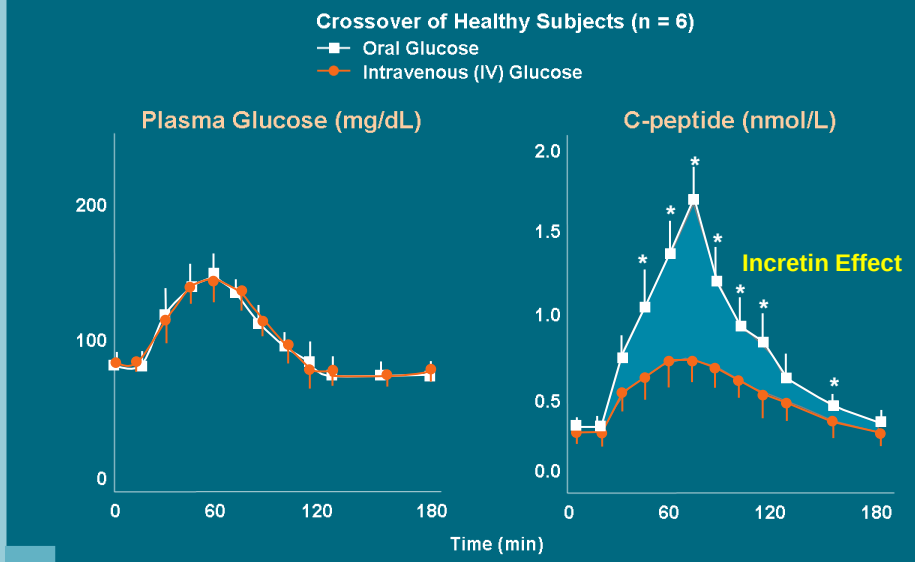
Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520
Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422
Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553
Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169

Glucagon-Like Peptide-1 (GLP-1)
An Important Incretin Hormone

- The "incretin effect" started the search
- Incretins
  - Gut hormones that enhance insulin secretion in response to food
  - Glucose-dependent insulin secretion
- GLP-1
  - Secreted from L cells of the small intestine
  - Most well-characterized incretin
  - Diminished in type 2 diabetes
- Glucagon
  - Secreted from pancreatic alpha cells
  - Counterregulatory hormone to insulin
  - Elevated in type 2 diabetes

Adapted from Aronoff SL, et al. *Diabetes Spectrum.* 2004;17:183-190

The Incretin Effect
Beta-Cell Response to Oral vs IV Glucose



Mean (SE); *$P \leq 0.05$
Data from Nauck MA, et al. *J Clin Endocrinol Metab.* 1986;63:492-498

The Beginning

- Exenatide
  - Synthetic version of salivary protein found in the Gila monster
  - More than 50% overlap with human GLP-1
    - Binds to known human GLP-1 receptors on beta cells (*in vitro*)
    - Resistant to DPP-IV inactivation

Exenatide	H G E G T F T S D L S K Q M E E E A V R L F I E W L K N G G P S S G A P P P S-NH_2
GLP-1 Human	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R-NH_2

↑ Site of DPP-IV Inactivation

- Following injection, exenatide is measurable in plasma for up to 10 hours

Adapted from Nielsen LL, et al. *Regul Pept.* 2004;117:77-88
Adapted from Kolterman OG, et al. *Am J Health-Syst Pharm.* 2005;62:173-181

Exenatide Mimics Many Properties of GLP-1

	GLP-1	Exenatide
↑ Glucose-dependent insulin secretion	✓	✓
↓ Glucagon secretion ↓ Hepatic glucose output	✓	✓
Regulates gastric emptying ↓ Rate of nutrient absorption	✓	✓
↓ Food intake	✓	✓
↓ Plasma glucose acutely to near-normal levels	✓	✓
Resistant to DPP-IV degradation		✓
Duration in plasma following a subcutaneous (SC) injection	Short	Long

See Important Safety Information included in this presentation

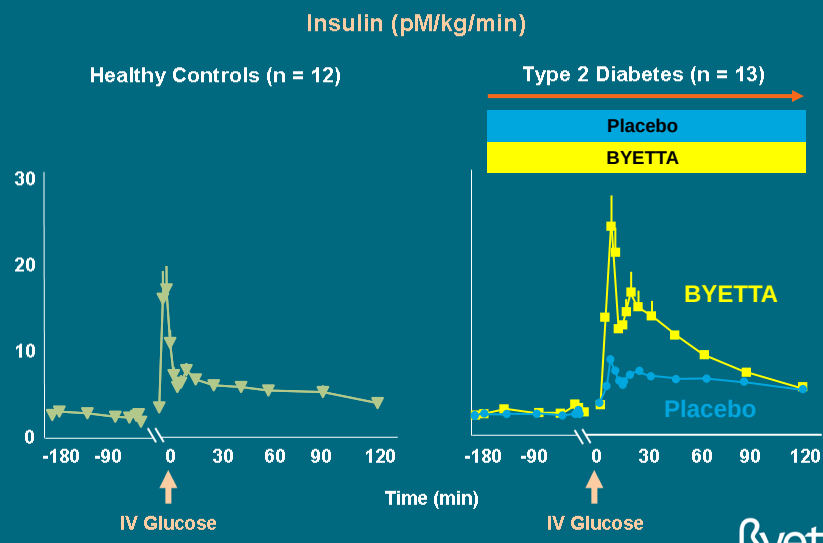
Leveraging the Therapeutic Potential of GLP-1

- GLP-1
  - Short half-life (<2 minutes)
    - Rapidly degraded by dipeptidyl peptidase-IV (DPP-IV)
- DPP-IV inhibition
  - Could extend endogenous GLP-1 half-life
- Incretin mimetics
  - Mimic many of the glucoregulatory effects of GLP-1
  - Resistant to DPP-IV
    - GLP-1 analogs
    - Exenatide

Byetta™ exenatide injection

See Important Safety Information included in this presentation
Adapted from Drucker DJ. *Diabetes Care.* 2003;26:2929-2940

Acutely Improving Beta-Cell Response
BYETTA Restored First-Phase Insulin Response



Byetta™ exenatide injection

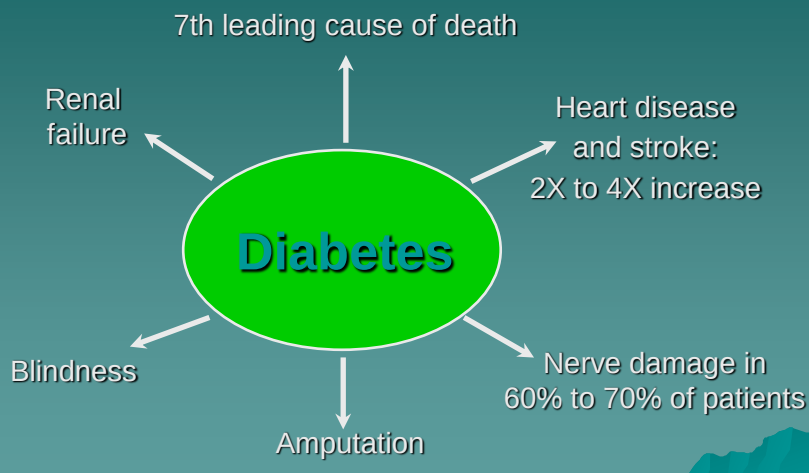
See Important Safety Information included in this presentation
Mean (SE); Evaluable
Data from Fehse F, et al. *Diabetologia.* 2004;47(suppl 1):A279

Summary of Pathophysiology

- **Type 1 diabetes**
  - The main abnormality is insulin deficiency
- **Type 2 diabetes**
  - Both insulin deficiency and insulin resistance contribute
- **Glucotoxicity and lipotoxicity**
  - Poor metabolic control worsens insulin deficiency and insulin resistance

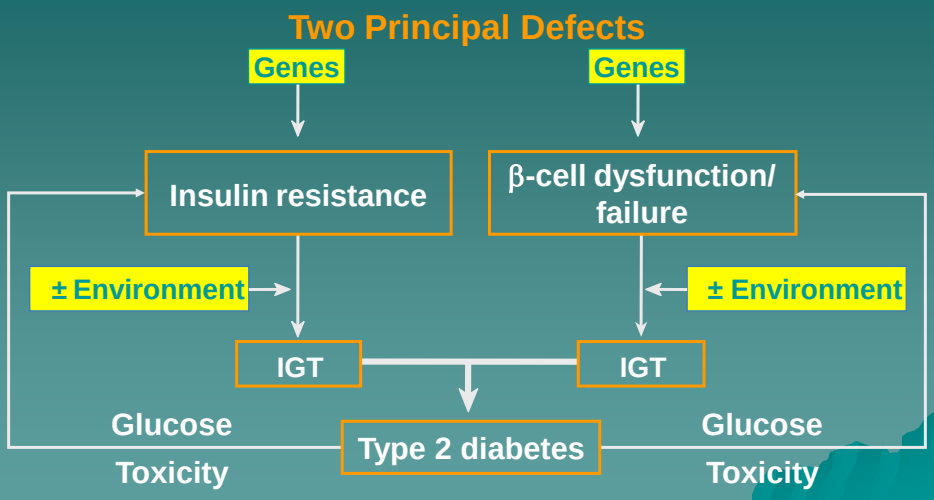
CAIDRE

Diabetes Mellitus in the US: Health Impact



Diabetes Statistics. March 1999. NIDDK publication NIH 99-3892; Harris MI, et al. *Diabetes Care*.

Type 2 Diabetes



Reaven GM. *Physiol Rev.* 1995;75:473-486; Reaven GM. *Diabetes/Metabol Rev.* 1993;9(Suppl 1):5S-12S; Polonsky KS. *Exp Clin Endocrinol Diabetes.* 1999;107 Suppl 4:S124-S127.

Prevention

- Diabetes Prevention Trial
  - Participants had signs of early insulin resistance
  - Three treatment strategies
    - Education alone
    - Medication (insulin sensitizer)
    - Increase physical activity
  - Exercise had greater impact than Rx
    - Type and frequency of exercise

CURRENT AMERICAN DIET

In **1970** Americans spent
$6 Billion on Fast Food
In **2000** Americans spent
$110 Billion on Fast Food
that is more than Higher Education, Personal Computers,Software, Movies, Videos & Recorded Music Combined!

ARE VITAMINS THE ANSWER?

In the 1960's the availability and use of vitamins increased. It seemed to make sense in correcting our nutritional problems.

What do we know about vitamins?

WHAT ARE VITAMINS?

- Described as "key nutrients" in food
- Deficiencies associated with disease
- Synthetic forms easily manufactured

Vitamin Deficiencies

- Vitamin A: loss of night vision
- Vitamin B: dry scaly skin, inflammation
- Vitamin C: scurvy, vascular fragility, fatigue, increased susceptibility to illness
- Vitamin D: fragile bones
- Vitamin E: infertility, miscarriages

SO IF WE REPLACE THESE MISSING OR LACKING VITAMINS, WILL WE ELIMINATE THESE PROBLEMS ?

- Isolated or synthetic vitamins have not consistently shown reversal of these problems.
- Surprisingly, there is a lot of emerging research showing safety concerns of vitamins.

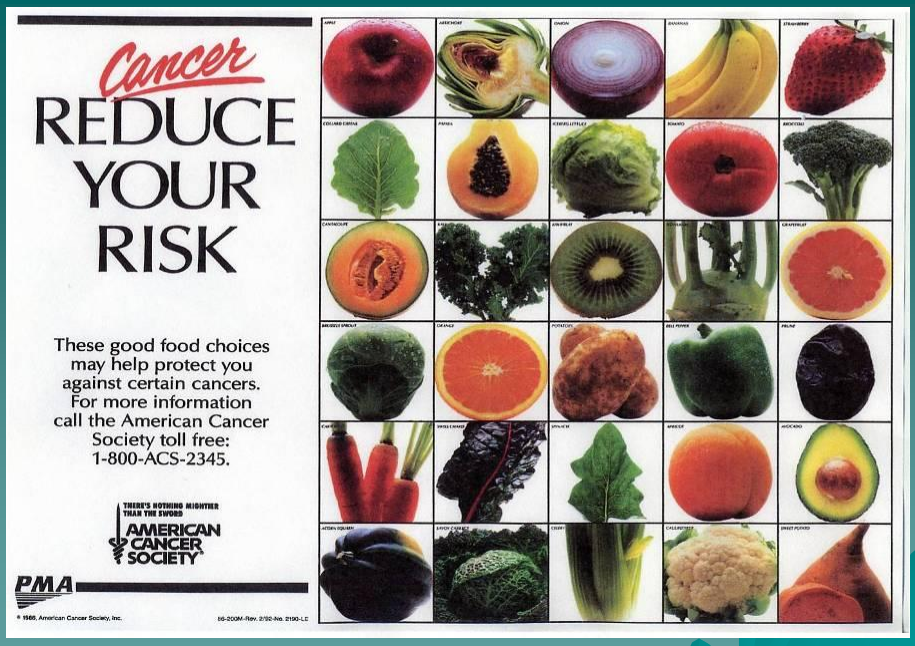
SOME ANTIOXIDANT SUPPLEMENTS LINKED TO LETHALITY.

JAMA 2007; 297: 842-857

This study only included vitamin supplements and these findings should not be translated to potential effects of fruit and vegetable sources of similar vitamins.

WHOLE FOODS ARE BEST.

- NUTRIENTS IN FOODS ARE BEST
  JAMA JULY 20, 2005
- ESSENTIAL NUTRIENTS: FOOD OR SUPPLEMENTS, WHERE SHOULD THE EMPHASIS BE?
  JAMA, 2005; 294: 351- 58



STUDY RESULTS

- MEDITERRANEAN DIET:
  - LENGTHENS LIFE

    British Medical Journal April 8, 2007
  - DECREASES ALZHEIMER'S

    Arch Neurol. 2006; 63: 1402-08

MEDITERRANEAN DIET

- Fruit, veggies, berries
- Whole grains, nuts, seeds
- Legumes, eggs, sheep and goat cheese
- Olive oil and avocado
- Lean meats and fish
- Moderate red wine

Fruits & Vegetables

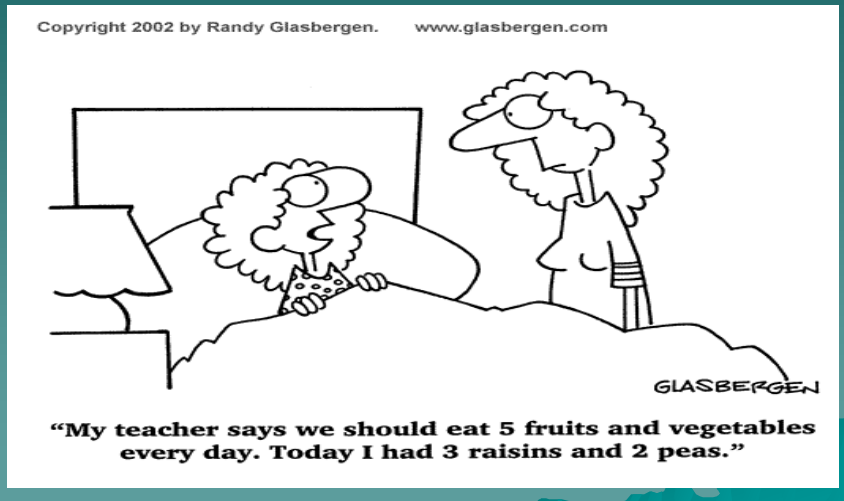
- Fruits and Veggies contain all the Vitamins, Minerals, Anti-oxidants, Phytonurients, enzymes that our bodies need every day – we need them in a rainbow of color.

USDA Guidelines

The new USDA guidelines
9-13 Servings
of Fruits and Vegetables a day!

- www.mypyramid.com

USDA Guidelines



Biggest Health Challenges Today

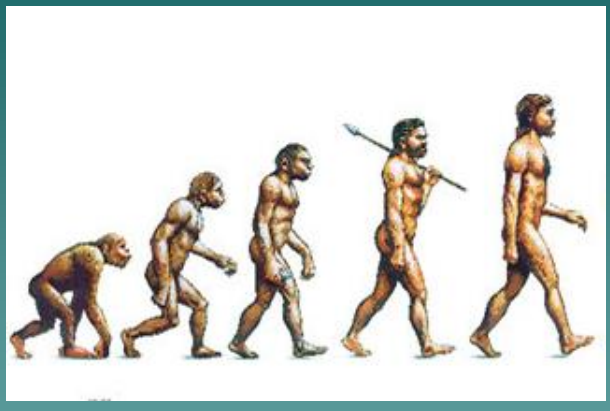
- **We are not eating enough Fruits & Vegetables**
- **Lower nutrient content in F&V today**
- **Food Prep – Folate and Folic Acid are destroyed in cooking.**
- **Accept health consequences of poor nutrition**

WHOLE FOOD SUPPLEMENTS

- They are fruit and vegetable juices processed carefully into a powder concentrate and then usually put into a capsule or tablet form.
- They are considered a 'food' and are labeled as food and not as a 'supplement' – thus do not contain isolated, synthetic or fragmented vitamins or minerals.

WHOLE FOOD SUPPLEMENTS

- Can help bridge the gap between what we should eat and what we do
- For more information:
  - www.ejlovesjuiceplus.com



andthe

The shape of things to come