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M E D I C I N E

# Why Are Diabetes and Depression Associated?

## Connecting the Brain to the Pancreas

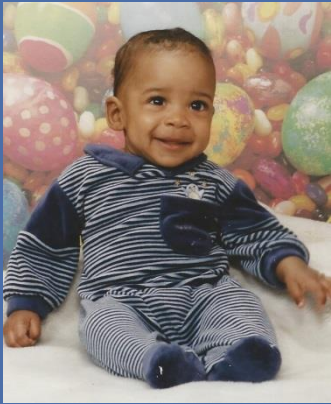
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Division of Endocrinology, Diabetes, and Metabolism

Welch Center for Prevention, Epidemiology, and Clinical Research

# Birth of a Research Career



San Antonio, TX  
American Diabetes Association  
Meeting 2000



Dr. Fred Brancati

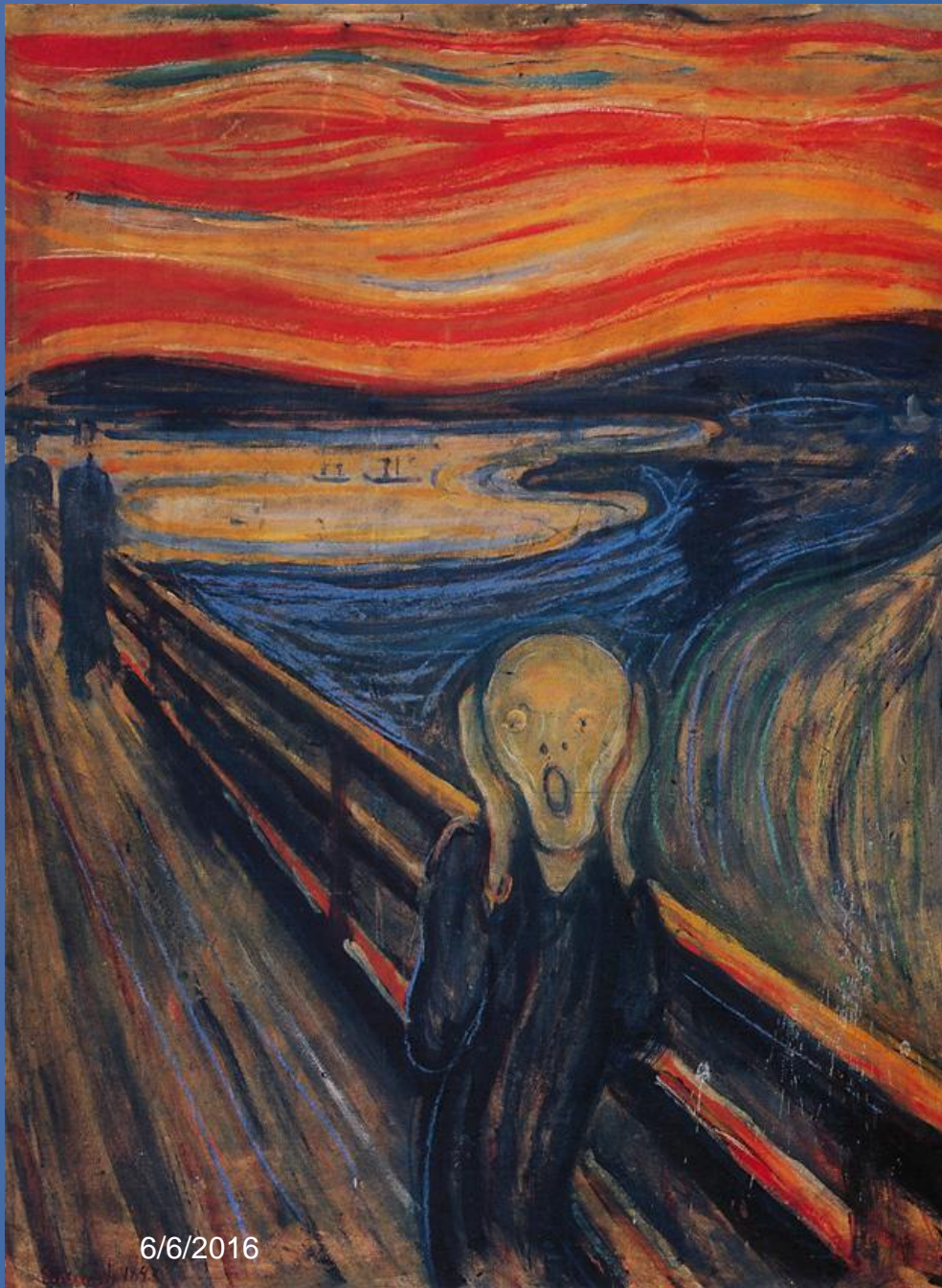


**STRESS**



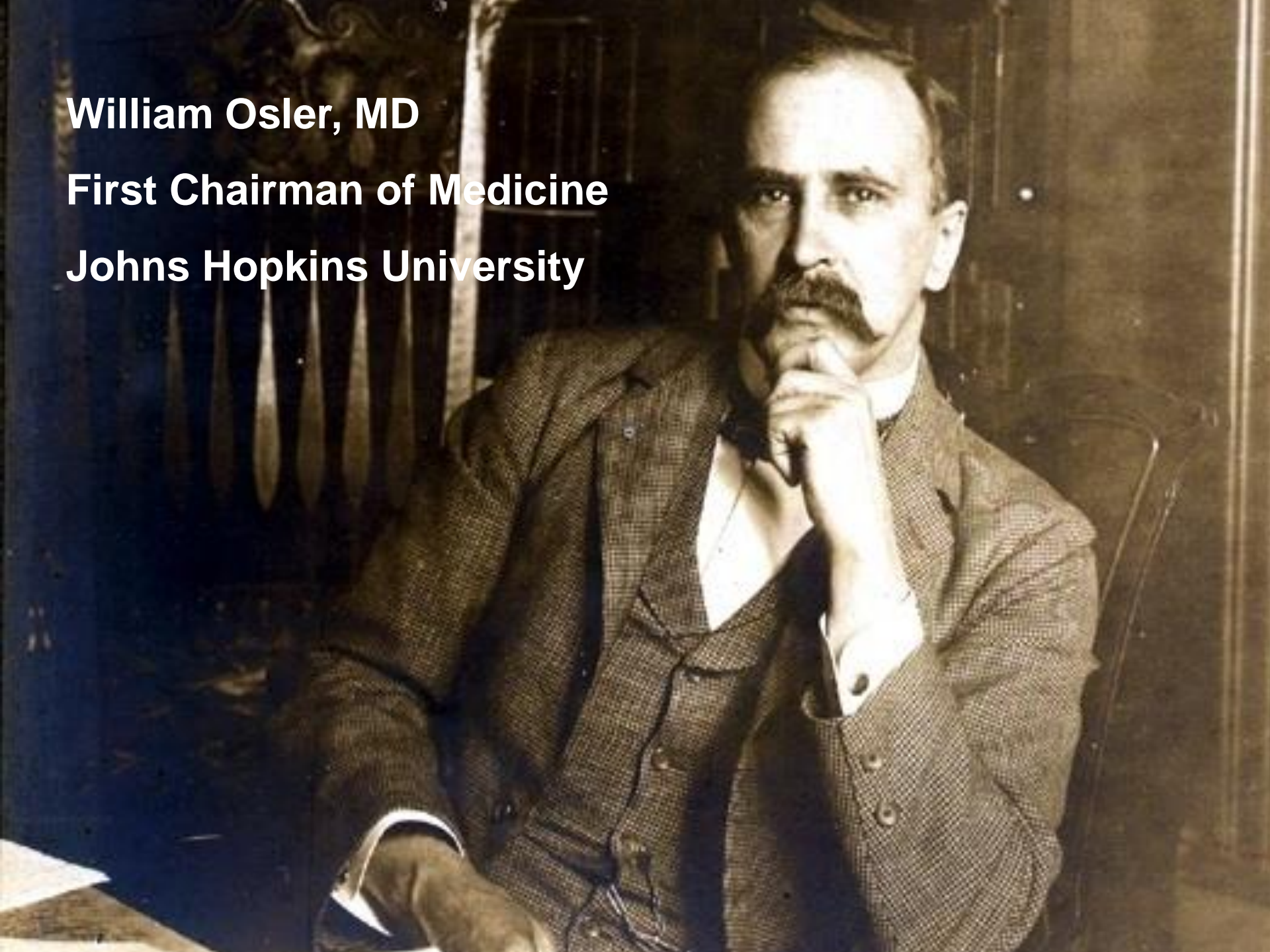
**STRESS**

Edvard Munch,  
1893



- You added bleach to the color load by accident!
- You woke up at the time you were supposed to be leaving for work!
- Most of your writers have not submitted their articles for a pending deadline!

**William Osler, MD**  
**First Chairman of Medicine**  
**Johns Hopkins University**



# Risk Factors for Type 2 Diabetes

## Osler's Principles & Practice of Medicine, 1892



- Heredity
- Ethnicity
- Social Class
- Adiposity
- Sedentary life
- Overindulgence

- Nervous strain
- Worry

**STRESS**

**STRESS**



# Diabetes and Depression: A Common Association In Adults



- Aggregate odds ratio of depression in adults with diabetes compared to those without diabetes: 2.0 (95% CI: 1.8, 2.2)
- Lifetime prevalence of major depression higher in individuals with diabetes (17.5%) compared to those without diabetes (6.8%)

Anderson et al. Diabetes Care, 2001

# Diabetes and Depression: A Common Association in Adolescents

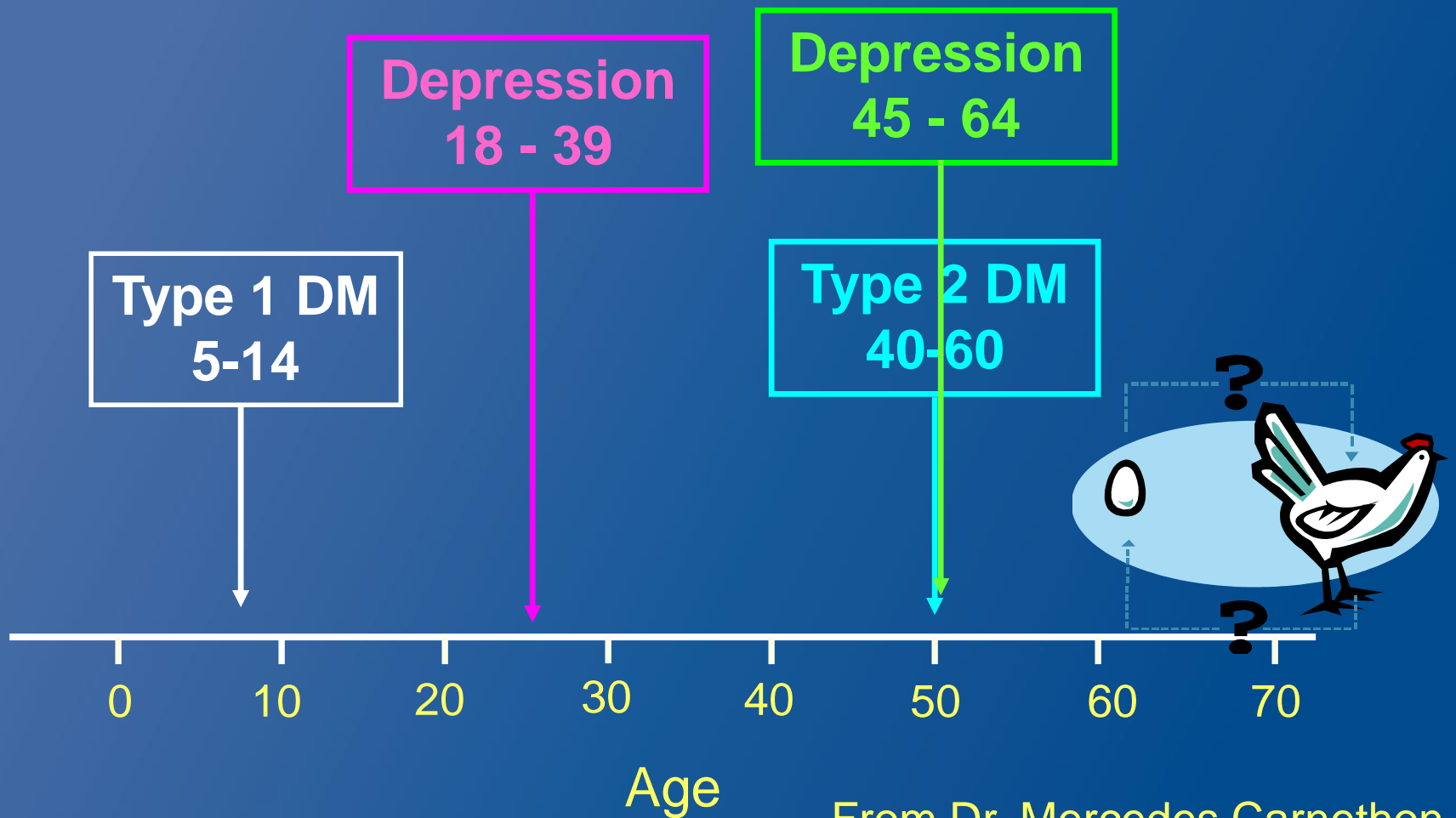


- 15-20% of adolescents with type 1 diabetes have elevated depressive symptoms
- 23% have subclinical depressive symptoms
- SEARCH Study: rates similar for type 1 and type 2 diabetes, but slightly higher in type 2

Kovacs et al., 1997; Grey et al, 2002; Hood et al., 2006; McGrady et al., 2009; Lawrence et al., 2006



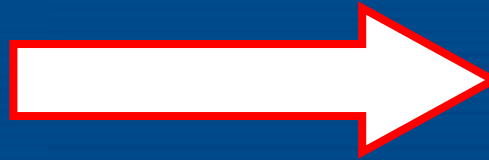
# Average Ages of Onset for Diabetes and Depression





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Diabetes mellitus



**DEPRESSION**

# Psychological demands imposed by diabetes

**DIABETES**

**New complications**

**Multiple complications**

Visual impairment

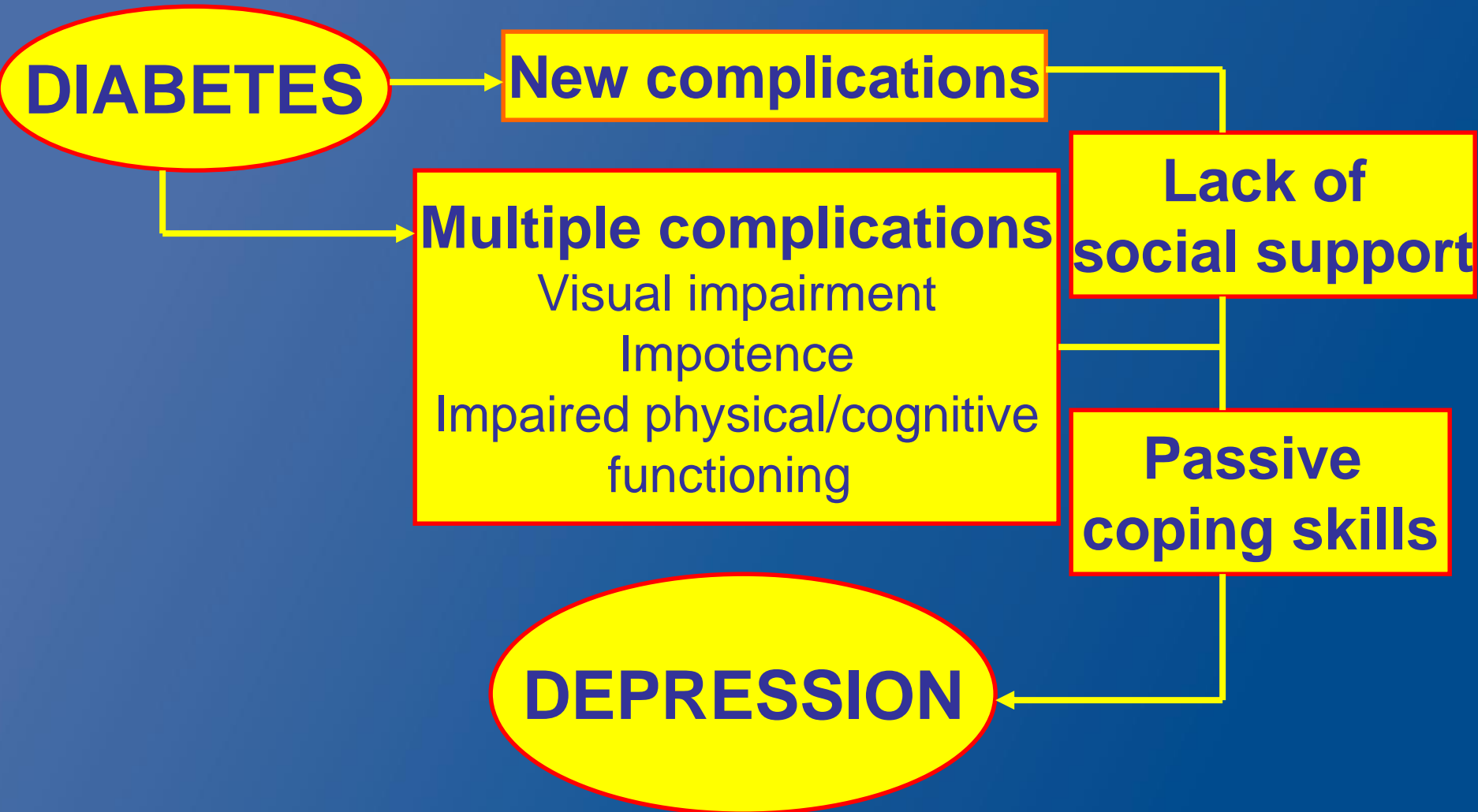
Impotence

Impaired physical/cognitive  
functioning

**Lack of  
social support**

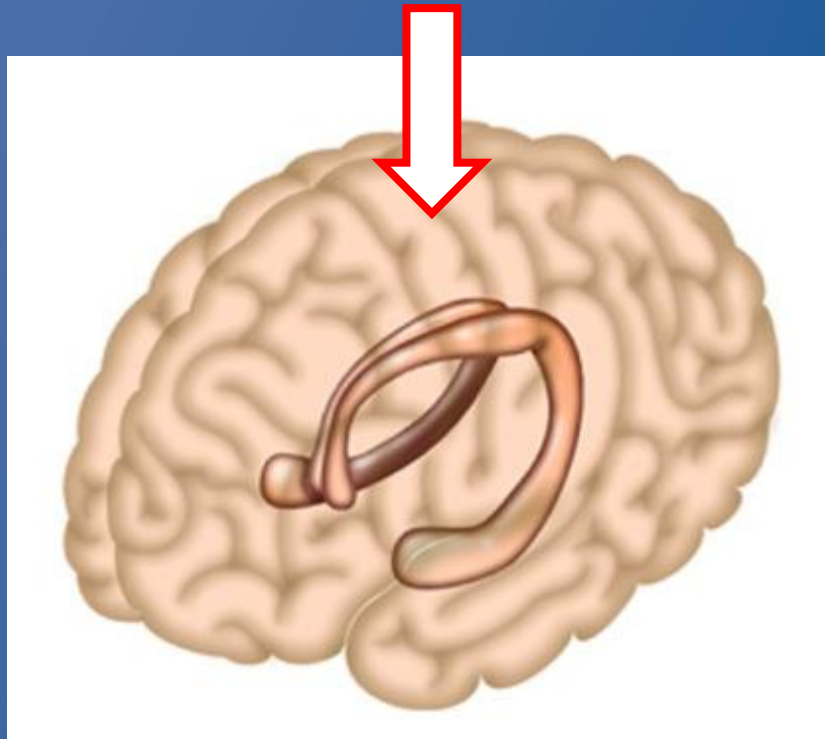
**Passive  
coping skills**

**DEPRESSION**



# Hyperglycemia associated with diabetes

## HYPERGLYCEMIA



- Adverse effects on hippocampus
  - Atrophy
  - Neuronal apoptosis
- Brain region that controls mood and cognition

# Description of the Multi-Ethnic Study of Atherosclerosis (MESA)



- Multi-center, longitudinal cohort study of occurrence and correlates of subclinical CVD and factors influencing its progression
- Six centers: Northwestern University, Wake Forest University, University of Minnesota, Columbia University, Johns Hopkins University, University of California-Los Angeles
- 6,000 men and women aged 45-85 years
  - 40% non-Hispanic White
  - 10% Chinese American
  - 30% African American
  - 20% Hispanic American
  - No history of clinical CVD

# MESA: Diabetes Depression

Visit 1  
00-02



Visit 2  
02-04



Visit 3  
04-05

4, 847 adults  
ages 45 to 84 w/o  
prevalent  
depression or  
CHD



Depression  
CES-D $\geq$ 16 and/or  
anti-depressant use

## Glucose Status

Normal fasting glucose (NGT)  
Impaired fasting glucose (IFG)  
Untreated DM  
Treated DM



# Diabetes Predict Development of Depression

- Individuals with diabetes at baseline had a 50% higher risk of developing depression during follow-up compared to those without diabetes
- Independent of differences in diabetes complications, socioeconomic status, and obesity



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Depression



DIABETES  
MELLITUS



# DEPRESSION

Psychosocial  
burden of illness,  
social support

Treatment  
Serotonin reuptake inhibitors  
Tricyclics

Behavioral  
smoking, diet, physical  
activity,  
treatment adherence

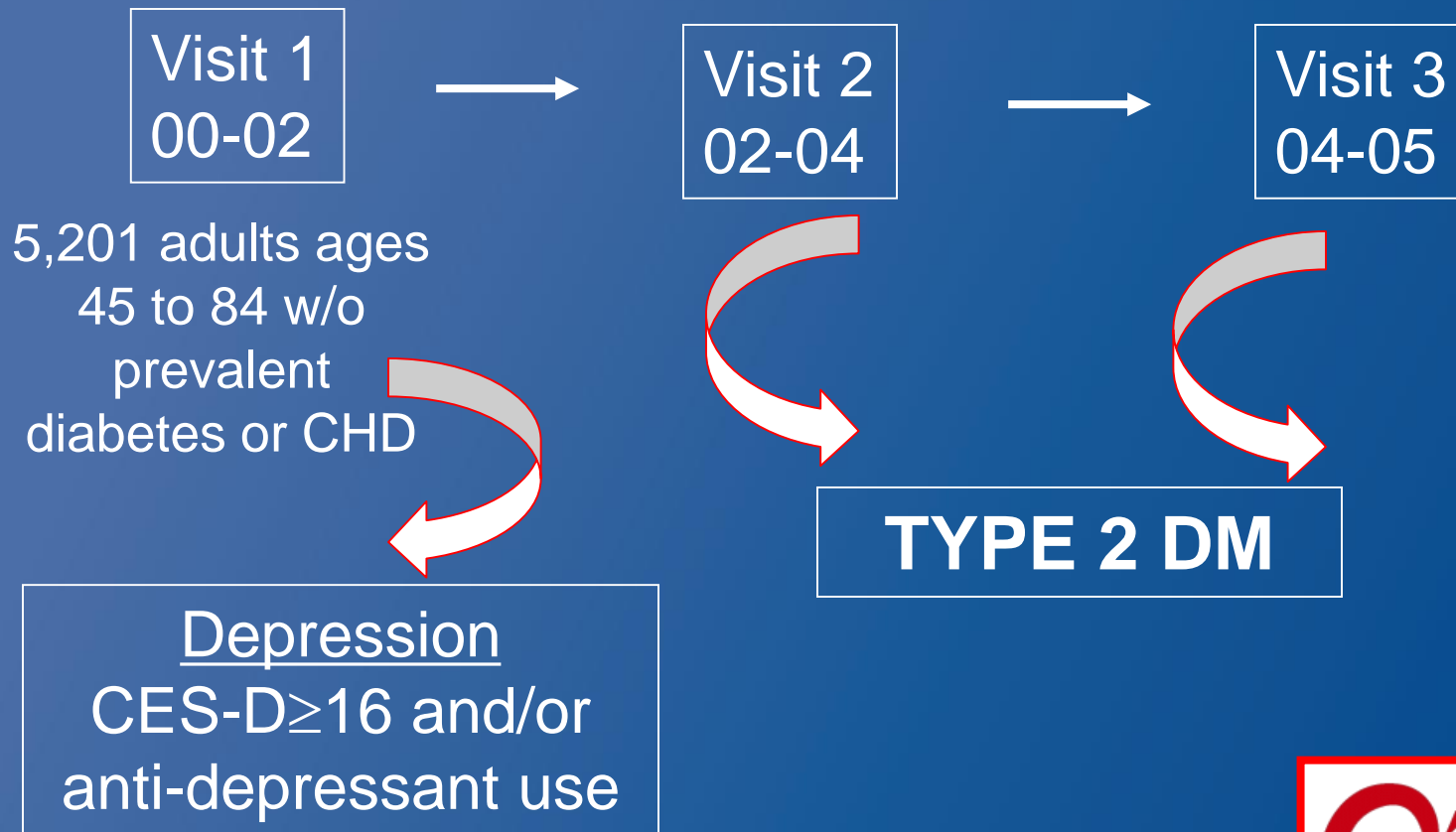
Neurohormonal  
↑cortisol, ↑catecholamines,  
↑inflammatory markers

## OBESITY

## INSULIN RESISTANCE

## TYPE 2 DIABETES

# MESA: Depression → Diabetes



# Depression Predicts Development of Diabetes

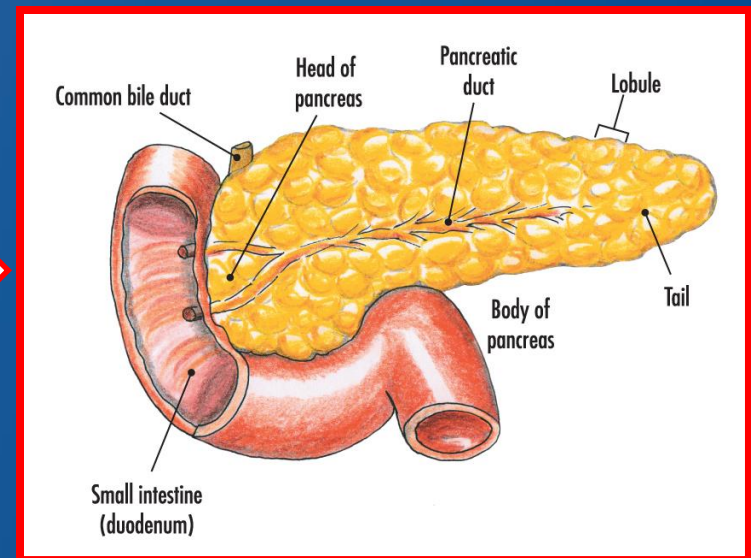
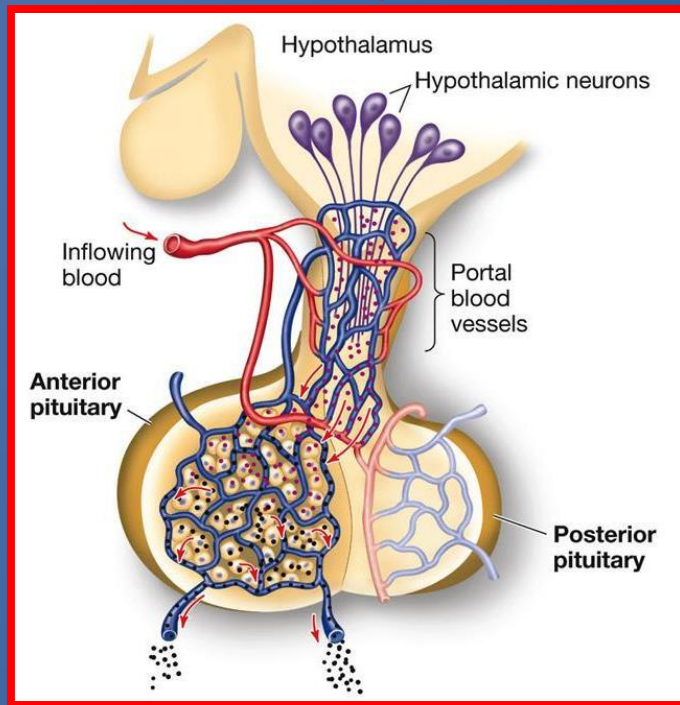
Depression was associated with type 2 diabetes risk factors:

- Less physical activity
- Greater calorie intake
- Higher likelihood of current smoking
- Higher body mass index
- High levels of inflammatory markers

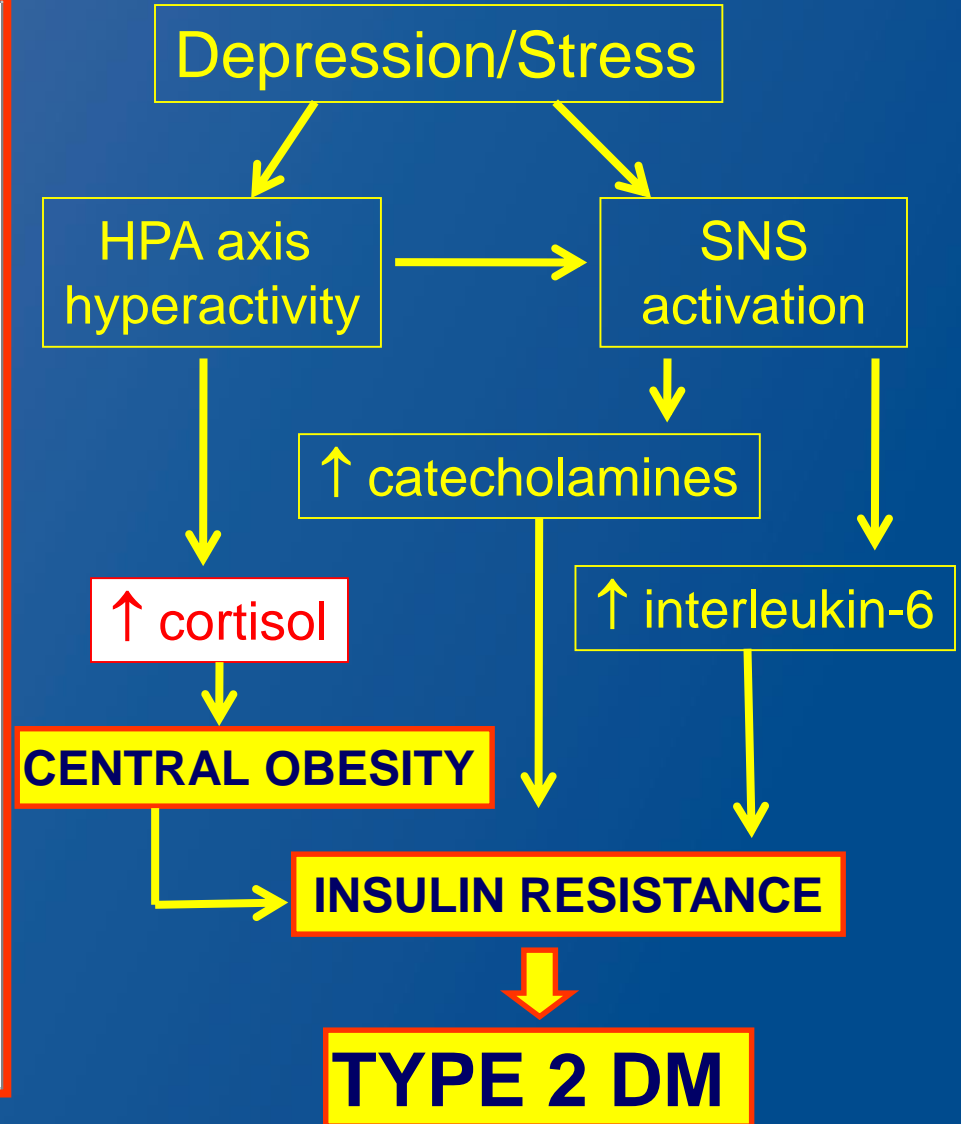
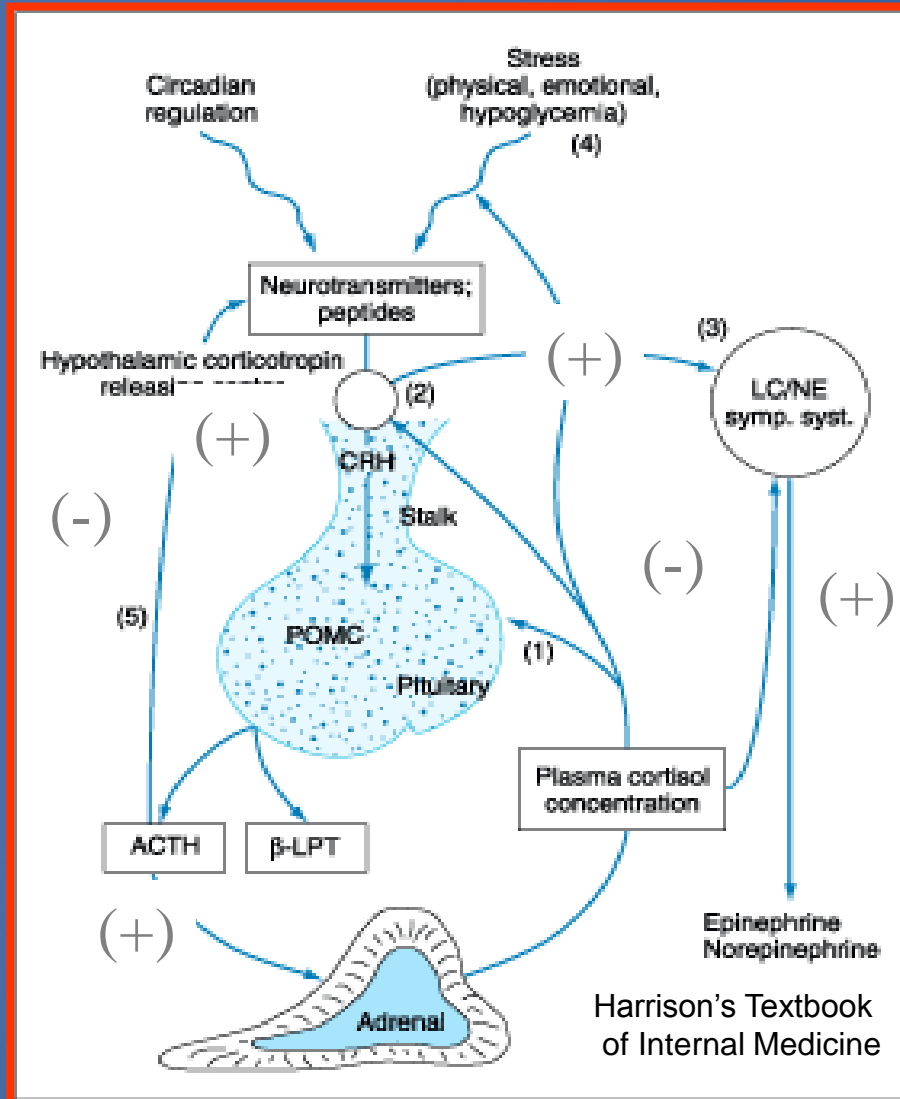
After controlling for these factors, depression was associated with a 21% higher risk of developing type 2 diabetes



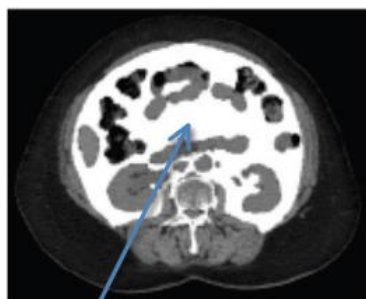
# Linking the Brain and Pituitary to the Pancreas?



# Stress affects hormonal factors that increase diabetes risk

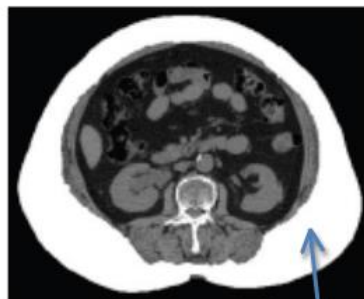


# Metabolic Perils of Central Obesity



(a)

Visceral Adipose Tissue



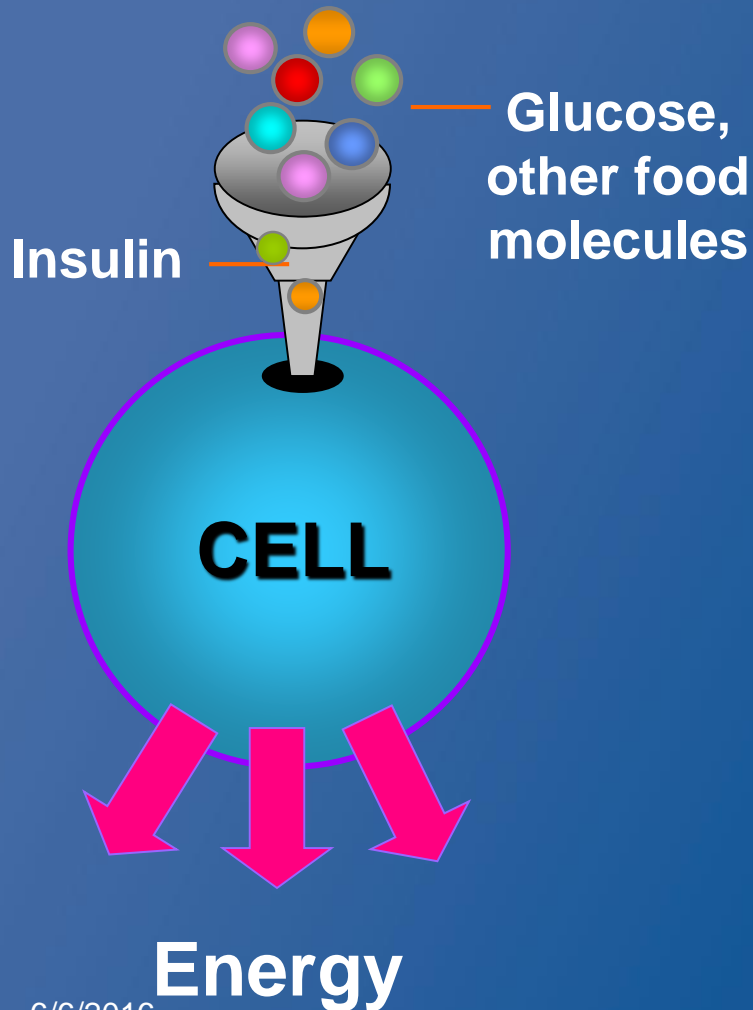
(b)

Subcutaneous Adipose Tissue

- ↑ glucose and insulin resistance
- ↑ blood pressure
- ↑ dyslipidemia (high triglycerides, low HDL)
- Risk for developing type 2 diabetes

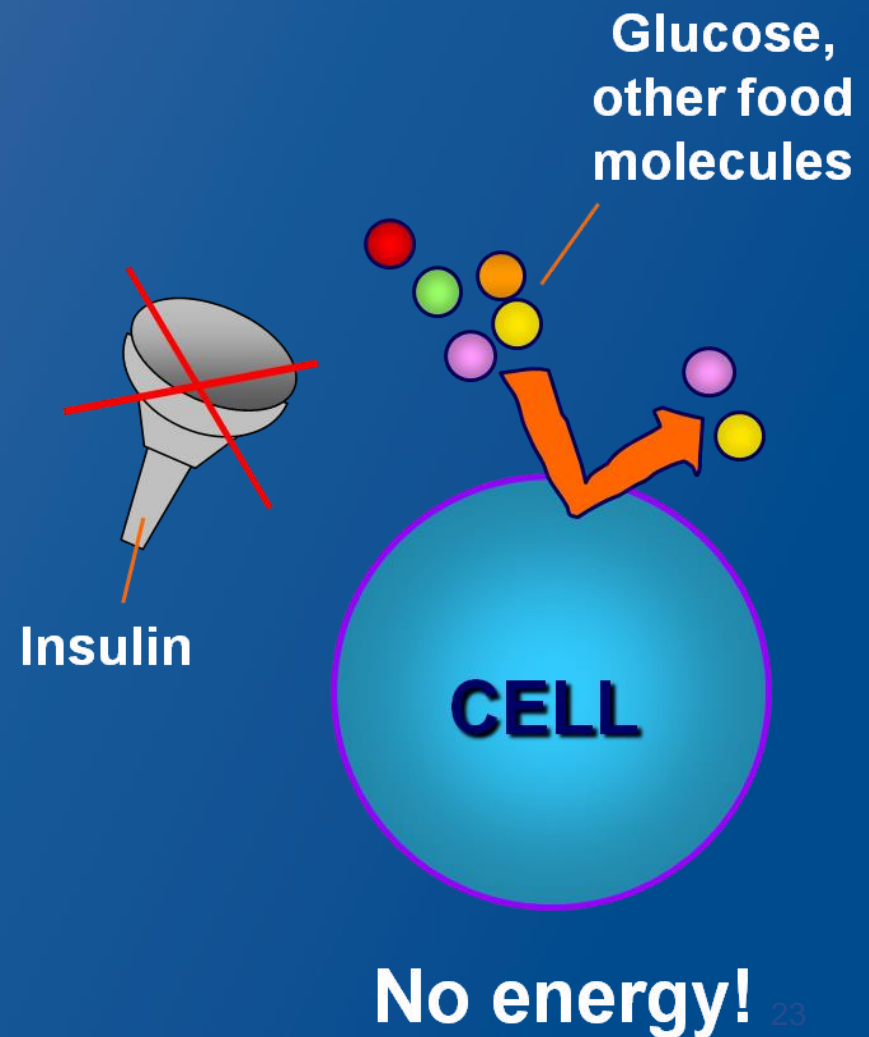
# Insulin Regulates Glucose Metabolism

## Normal insulin action



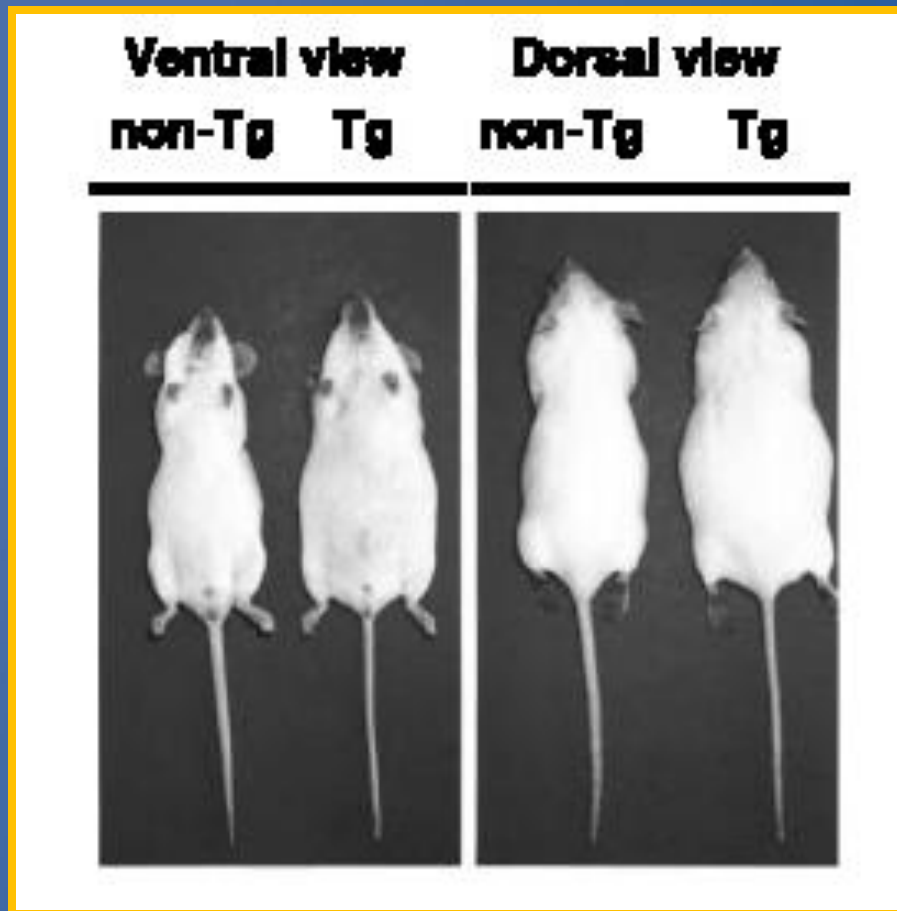
6/6/2016

## Abnormal insulin action



# Cortisol Hypothesis: Animal Data

11  $\beta$  -HSD 1 inactive active cortisol

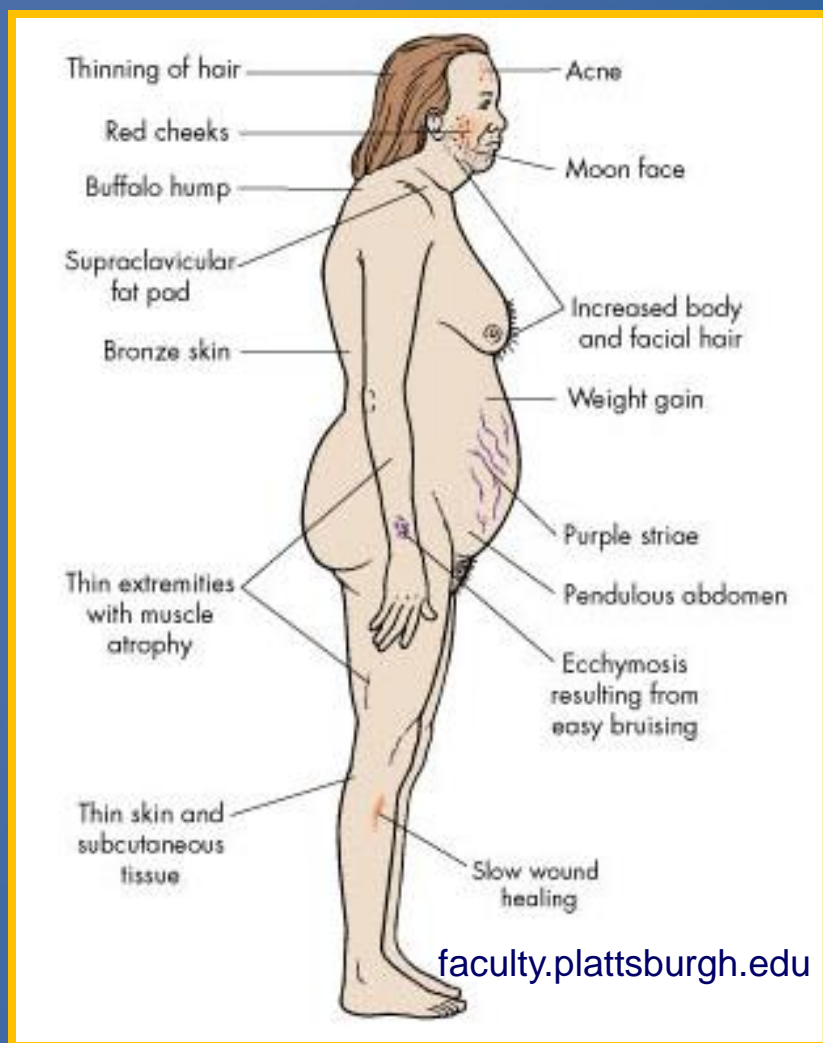


Transgenic mouse model of 11 $\beta$ -HSD1 overexpression

- Insulin resistance
- Obesity
- High cortisol in liver circulation



# Cortisol Hypothesis: Clinical and Human Research Data



- Overt hypercortisolism
  - Cushing's Syndrome
  - Steroid-induced diabetes
- Cortisol axis dysfunction independent of depression
  - Type 2 diabetes
  - Obesity

Champaneri et al, Metabolism, 2012

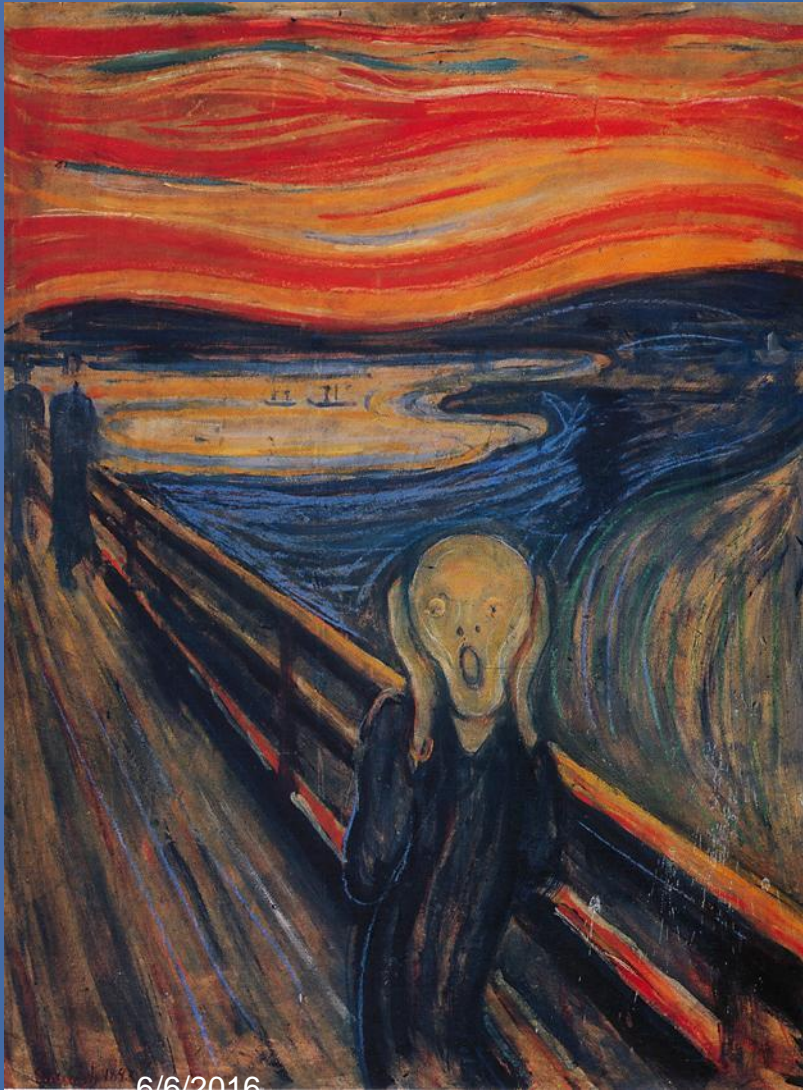
Champaneri et al, Obesity, 2013;

Joseph et al, Psychoneuroendocrinology, 2015

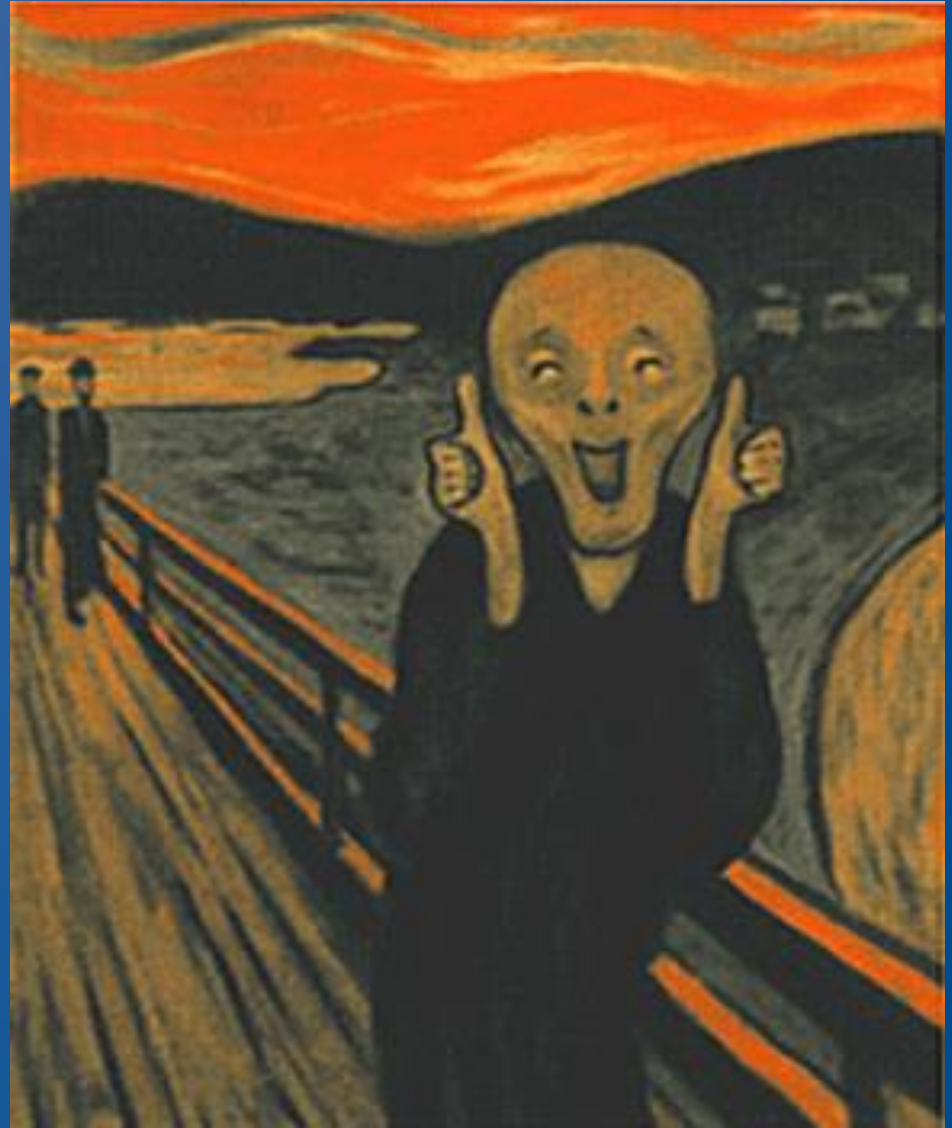
# So What? Significance and Future Directions



- Modification of the neurohormonal response: a novel approach to primary prevention of Type 2 diabetes (complementary to established measures)
- Collaborative care models that simultaneously treat depression and diabetes will likely improve outcomes for both conditions



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