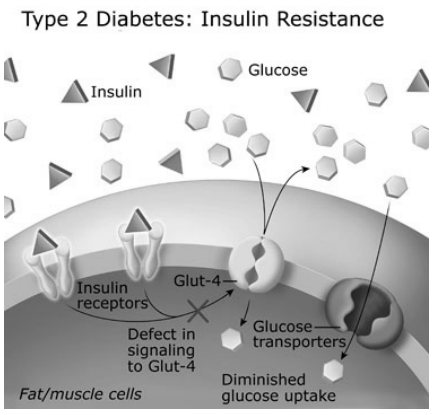
Developmental origins of disease – Joe Alcock MD Evo Med 2012

# EVOLUTION OF DIABETES

## Diabetes

- Insulin resistance
- Decreased glucose uptake
- Hyperglycemia



## Thrifty Genotype

- One of the earliest evolutionary medicine hypotheses
- Remember our discussion of traditional societies exposed to a Westernized diet?
- Some populations have astronomical rates of diabetes.

## Imagine an island population

- Two kinds of people on the island –
  - Some are large and lean, little energy storage, more growth.
  - Others are smaller and with more adipose reserves, and less energy used for growth and maintenance.

## Island Famine

- The second group might survive famine better, leaving more descendants
- Thrifty genotype
- Unpredictable food environment might select for thrifty genes
- May explain massive disparities in diabetes rates between different populations
- Genes that store fat and conserve energy. Insulin resistance.

## Thriftiness of Insulin

- Insulin promotes storage of fat
- Insulin promotes storage of glucose in liver

- Insulin resistance means higher insulin levels
- Insulin resistance means less growth and less fuel for muscles

# Overnutrition

- In adults obesity causes diabetes
- Gene-environment mismatch

- What about in infants?
  - birth weight was studied and an association with CVD was found.

## Thrifty Phenotype

- Reported that developmental factors play a role
- Individuals with the same genes can end up following one of two pathways:
  - No intrauterine stress – plentiful nutrition – no insulin resistance
  - Stress, inadequate nutrition – insulin resistance

## Developmental Origins of Adult Disease

- Risk of coronary disease correlates with BMI in adults
- Barker et al found opposite relationship in infants
- Diabetes has the same pattern – more in fatter adults, less in fatter infants

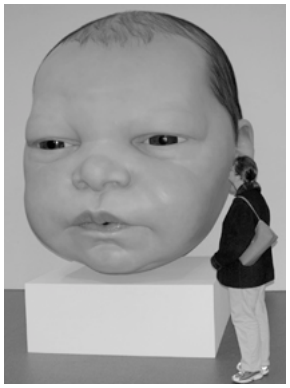
## Abdominal Fat…

## Fetal Undernutrition - Small Babies

- In response to poor nutrition, babies reduce their growth rate
- Stress induces other changes in physiology:
  - Lipid profile
  - Glucose metabolism
  - Blood pressure
  - Visceral fat storage

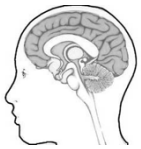
## Visceral fat – Free fatty acids

- Human babies have big brains
- Unlike muscles, the brain has fixed metabolic needs
- In nutritional stress, the brain needs fuel



## Visceral fat and Insulin resistance

- IR makes growth slow and increases glucose available for the brain
- Visceral fat mobilization causes free fatty acid release
- So in stressed and underfed infants/children the brain gets the fuel that it needs.



## Small for Gestational Age

- Preferentially deposit fat in visceral depot
- Short term energy balance
- Innervated by sympathetic nervous system
- Increased ability to respond to stress and to mobilize resources

## Metabolic Syndrome

- In addition to insulin resistance:
- Increased levels of free fatty acids
- Impaired relaxation of blood vessels
- Increased catecholamines (adrenalin)
- Increased storage of visceral fat
  - Saturated free fatty acids also provide fuel for the brain
  - Visceral fat can be mobilized much faster than subcutaneous fat

## Fetus senses environment

- Nutritional stress in utero
- Activates a "switch" that turns on insulin resistant/visceral fat phenotype
- Thrifty phenotype gamble
- Nutrient poor environment - no diabetes, no cardiovascular disease

## Diseases of Western Civilization?

- May represent a thrifty phenotype bad gamble
- Increasing rates of diabetes hypertension in developing world
- Smaller the infant the higher rate of later diabetes, inflammation, cardiovascular disease

## Tradeoffs

- Energy is finite
- Physiology and metabolism trade-offs

- What is the major source of mortality for small babies/toddlers?

## Undernourished children die from infections

- Most childhood deaths are from infectious diarrhea
- Peak in early infancy and at age 2
- In traditional societies, age 2 is time of weaning – breast milk cannot keep up with demand. Undernourished children are at high risk of death at this time.

American Journal of Clinical Nutrition, Vol. 80, No. 1, 193-198, July 2004

## Another benefit for insulin resistance?

- Blood glucose levels are higher
- Less glucose is metabolized by muscles, bone, and most growing tissues
- Some cells in the body are not dependant on insulin to metabolize glucose.
  - Brain
  - ***White blood cells***

## Insulin Resistance and Thriftiness

- Insulin resistance is part of a suite of metabolic changes with adaptive value during stressful events, such as famine or trauma
- "high cytokine responders" with IR and metabolic syndrome benefited in past. e.g Pima Indians after suffering epidemic infectious disease post –European contact.

Fernandez-Real, Ricart. Insulin resistance and inflammation in an evolutionary perspective: the contribution of cytokine genotype/phenotype to thriftiness. Diabetologia (1999) 42: 1367-1374

## IR blocks muscle glucose uptake

- Increases blood glucose
- Increases glucose availability for non-insulin dependent tissues: immune system, brain placenta and mammary gland.*
- This contributes to defense against pathogens

Fernandez-Rael. Genetic Predispositions to Low Grade Inflammation in Type II Diabetes. Diabetes Technology and Therapeutics2006. 8 (1):55-68

## Resource Allocation

- Immune cells
  - In times of stress and infection, metabolic requirements of white blood cells skyrockets
  - Do not require insulin dependent glucose shunt
- Insulin resistance has the effect of delivering more fuel to the immune system
- Perhaps insulin resistance is promotes survival of undernourished children from diarrhea.

## Short term vs Long term effects

- Short term – mild insulin resistance may help body fend off infection
- Long term – becomes full blown diabetes
- Immune function in diabetics is impaired and death from infection is increased!
- May be example of antagonistic pleiotropy

## Summary

- Thrifty genotype
- Thrifty phenotype
- Preservation of brain development
- Resistance to infection
- Antagonistic Pleiotropy