Diabetes and HHS: The Hyperosmotic Hyperglycemic Syndrome

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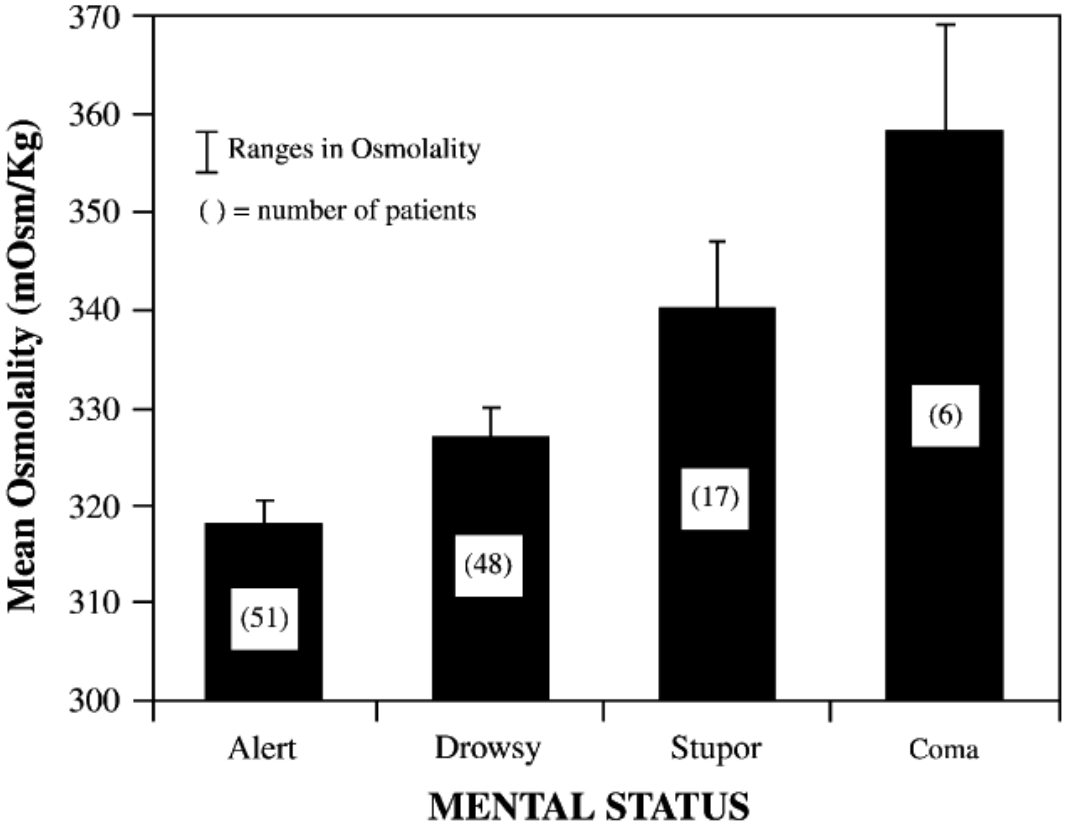
HHS…formerly known as

- Non-ketotic Hyperglycemic Coma
- Hyperosmolar Hyperglycemic Non-ketotic Syndrome
- Hyperosmotic Non-Ketotic State (HONK)
- Hyperglycemic Hyperosmolar Syndrome

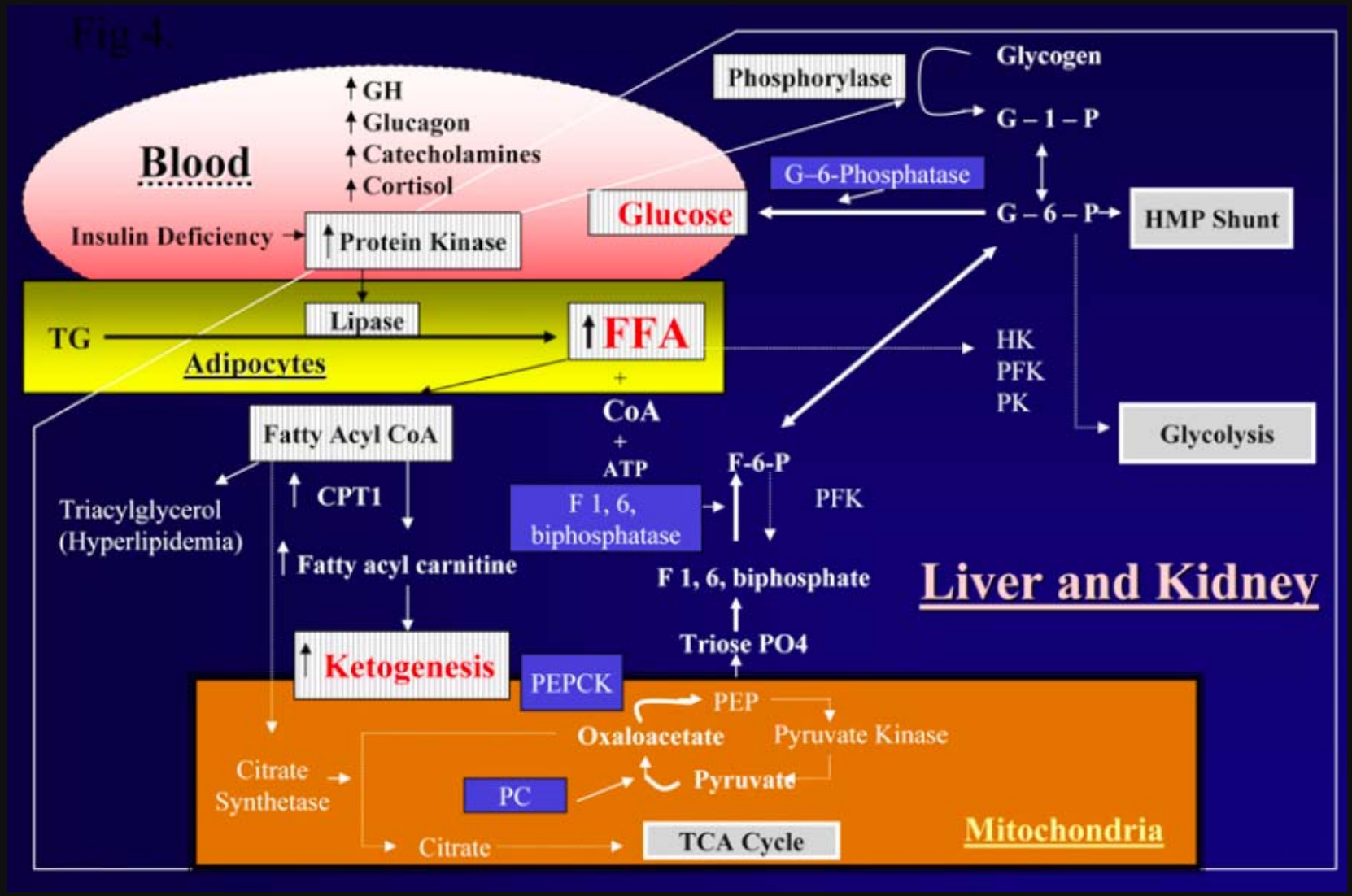
HHS: Why did ADA abandon…

Non-ketotic Hyperglycemic Coma

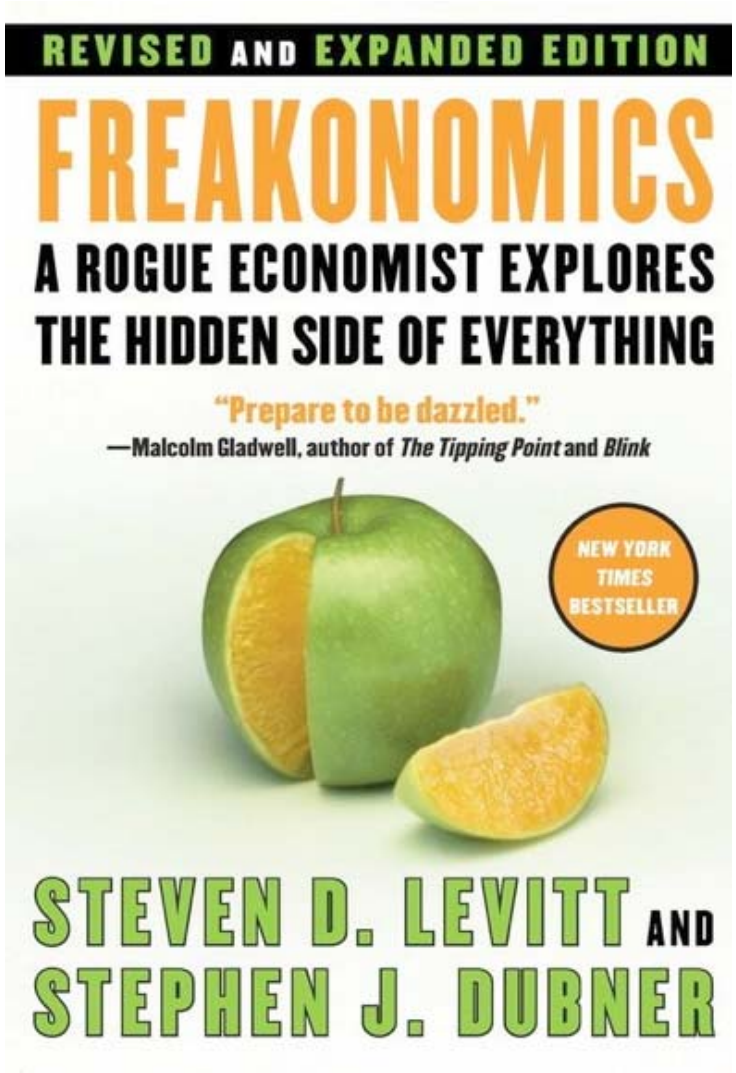
Mental status changes
23/122 (19%)

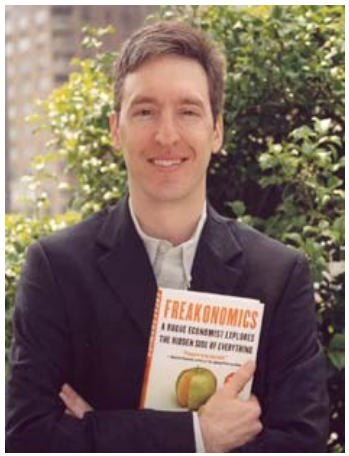


What to talk about ?



A pre pre-hospital talk…





So…

- Epidemiology
- Thrifty Genes
- Macroeconomic issues
- Differences from DKA
- Who gets into trouble & why?
- Patient Assessment
- Approaches to management

Question...

What are the 4 biggest risks associated with the development of Type 2 DM in the USA ?

1. & 2.

3. Genetic & Auto-Immune

4. The Farm Bill

At the root of the DM epidemic: The Farm Bill

- **Founder of the Farm Bill**
- ***Sec of Agriculture***
- ***Assistance program to subsidize poor farmers***
- ***$284 Billion subsidy (2008) Mega-Farm industry***
- **Non-sustainable corn,soy & wheat farming practices**
- **Impact on the American diet**

Henry Wallace…(1888-1965)

Agri-Farm Subsidies

Rank	Program (click for top recipients, payment concentration and regional rankings)	Number of Recipients 1995-2006	Subsidy Total 1995-2006
1	Corn Subsidies	1,568,095	$56,170,875,257
2	Wheat Subsidies	1,308,268	$22,051,566,200
3	Cotton Subsidies	247,879	$21,329,862,262
4	Conservation Reserve Program	768,180	$20,337,282,263
5	Disaster Payments	1,246,432	$15,114,518,393
6	Soybean Subsidies	985,712	$14,239,702,740
7	Rice Subsidies	65,533	$11,043,795,298
8	Sorghum Subsidies	586,766	$4,569,912,363
9	Dairy Program Subsidies	151,737	$3,560,356,847
10	Livestock Subsidies	754,842	$2,908,502,988
11	Peanut Subsidies	89,463	$2,609,286,072
12	Barley Subsidies	337,812	$1,962,025,270
13	Env. Quality Incentive Program	115,206	$943,955,199
14	Tobacco Subsidies	383,889	$530,488,022
15	Sunflower Subsidies	57,976	$461,135,751
16	Apple Subsidies	8,586	$261,540,987
17	Sugar Beet Subsidies	9,071	$242,064,005
18	Canola Subsidies	19,390	$200,281,433
19	Oat Subsidies	620,641	$198,255,252
20	Wool Subsidies	73,277	$185,590,080

So…how many calories will $2.00 buy your patient's

Subsidized crops

- 1100 Calories of cookies
- 1000 calories of chips
- 875 calories of soft drink
- 950 calories 39 ingredient Twinkie
- 1300 calories subsidized school lunch of chicken tenders and tater tots

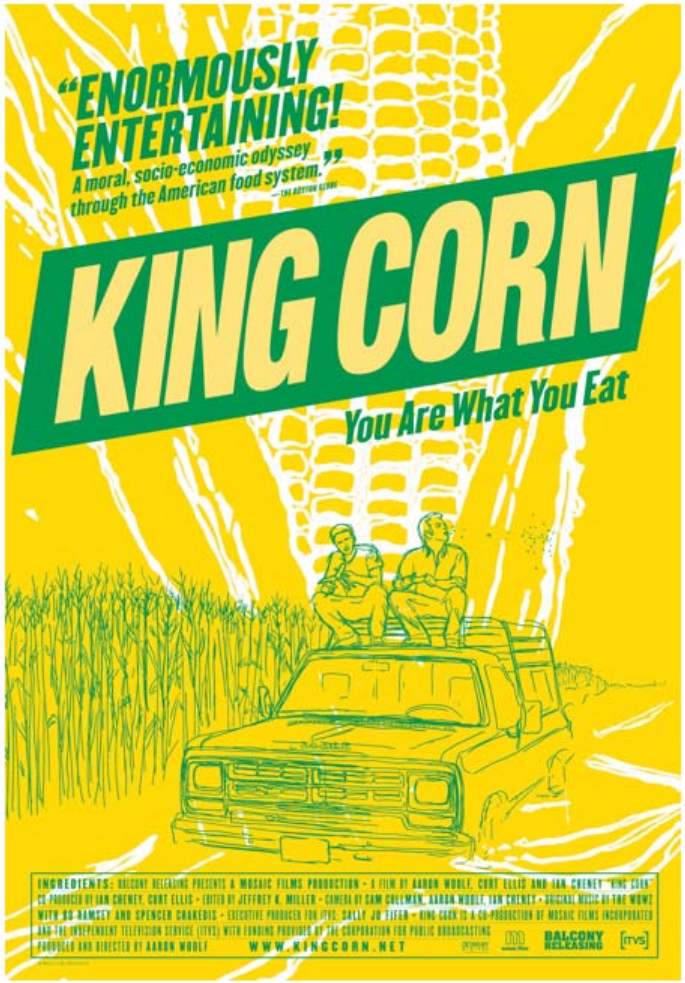
Non-Subsidized Crops

- 250 calories of carrots
- 322 calories avocado
- 170 calories of OJ
- 100 calories tomatoes
- 165 calories of almonds

King Corn…

"When meditating over a disease, I never think of finding a remedy for it, but, instead a means of preventing it ." *L. Pasteur 1884*

- **#1 crop 93 million acres**
- **9.4 Billion corn subsidy**
- **HF corn syrup #1**
- **Obesity ages 6-11**
- **Feedlot Obesity**
- **Cost of food**



Epidemiology of Diabetes

Type 1: 5 -10%

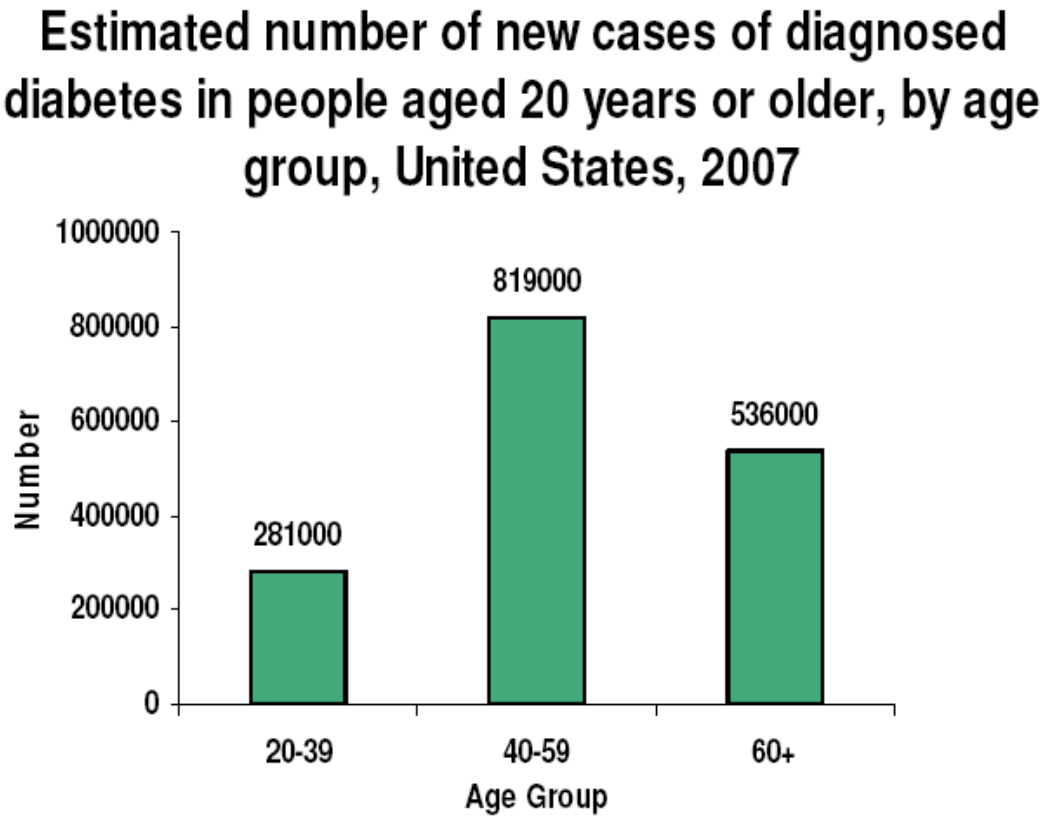
Type 2 : 90 - 95%

African Americans: 1.7 > than Caucasion

Poor twice that of the Affluent

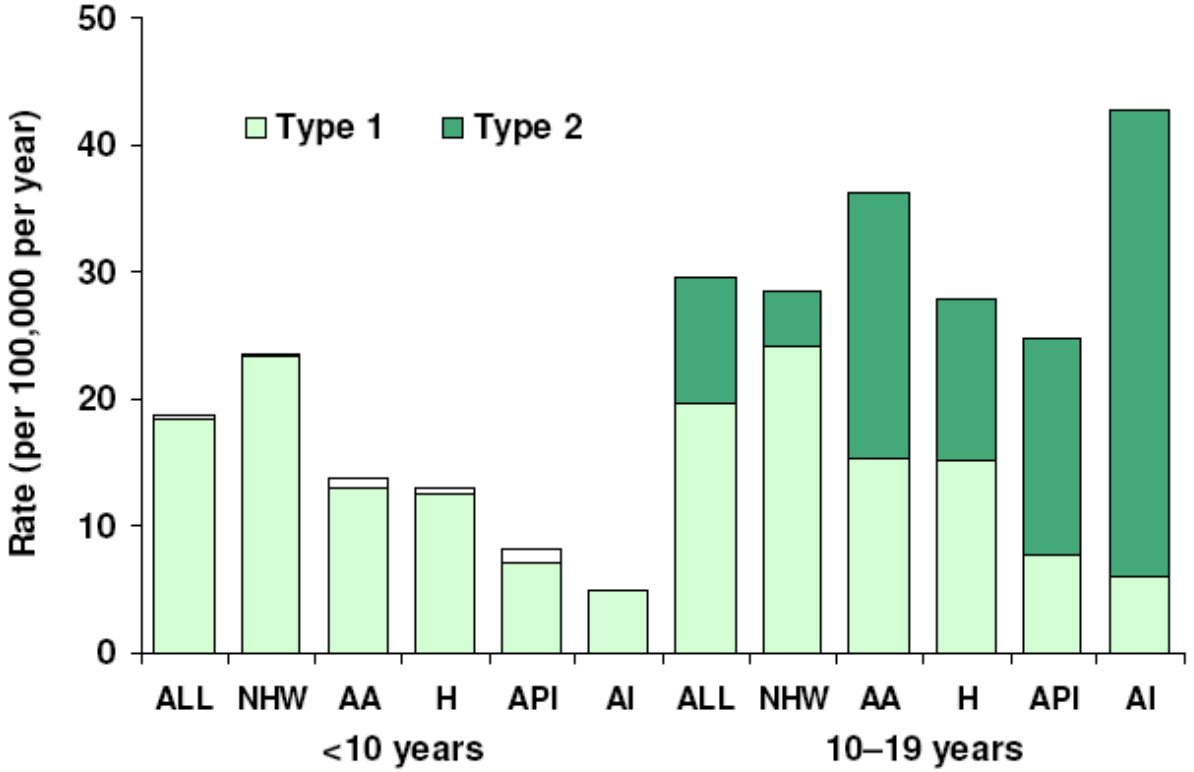
Prevalence is nearly doubling every decade in developed countries.

Prevalence by age



CDC. National Diabetes Fact Sheet, 2007.
Source: 2004–2006 National Health Interview Survey estimates projected to year 2007.

Rate of new cases of type 1 and type 2 diabetes among youth aged <20 years, by race/ethnicity, 2002–2003



CDC. National Diabetes Fact Sheet, 2007.
Source: SEARCH for Diabetes in Youth Study
NHW=Non-Hispanic whites; AA=African Americans; H=Hispanics; API=Asians/Pacific Islanders; AI=American Indians

Diabetes Mellitus: A "Thrifty" Genotype Rendered Detrimental by "Progress"?

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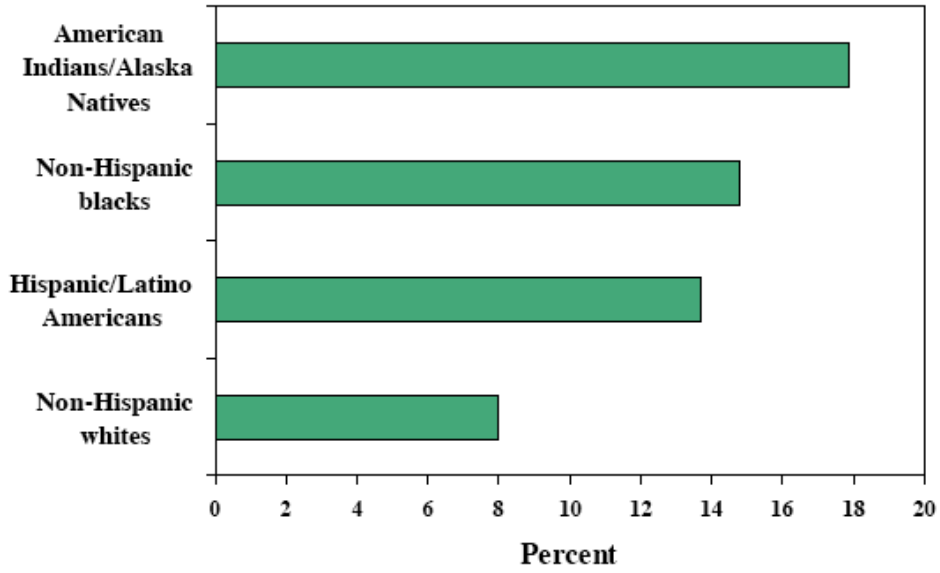
FOR THE POPULATION GENETICIST, diabetes mellitus has long presented an enigma. Here is a relatively frequent disease, often interfering with reproduction by virtue of an onset during the reproductive or even pre-reproductive years, with a well-defined genetic basis, perhaps as simple in many families as a single recessive or incompletely recessive gene (cf. Allan, 1933; Pincus and White, 1933, 1934; Harris, 1950; Steinberg and Wilder, 1952; Lamy, Frézal and de Grouchy, 1957; Steinberg, 1959; Post, 1962a). If the considerable frequency of the disease is of relatively long duration in the history of our species, how can this be accounted for in the face of the obvious and strong genetic selection against the condition? If, on the other hand, this frequency is a relatively recent phenomenon, what changes in the environment are responsible for the increase? Current developments in the study of this disease suggest an explanation with important biological ramifications.

"THRIFTINESS" OF DIABETIC GENOTYPE PRIOR TO ONSET OF DIABETES MELLITUS

Am J Hum Genet. 1962 December; 14(4): 353–362

Prevalence by ethnicity/economics “thrifty gene theory”

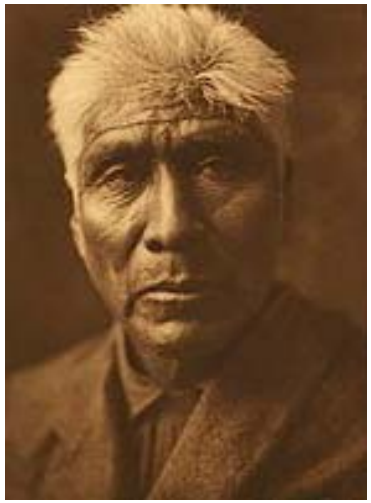
Estimated age-adjusted total prevalence of diabetes in people aged 20 years or older, by race/ethnicity—United States, 2005

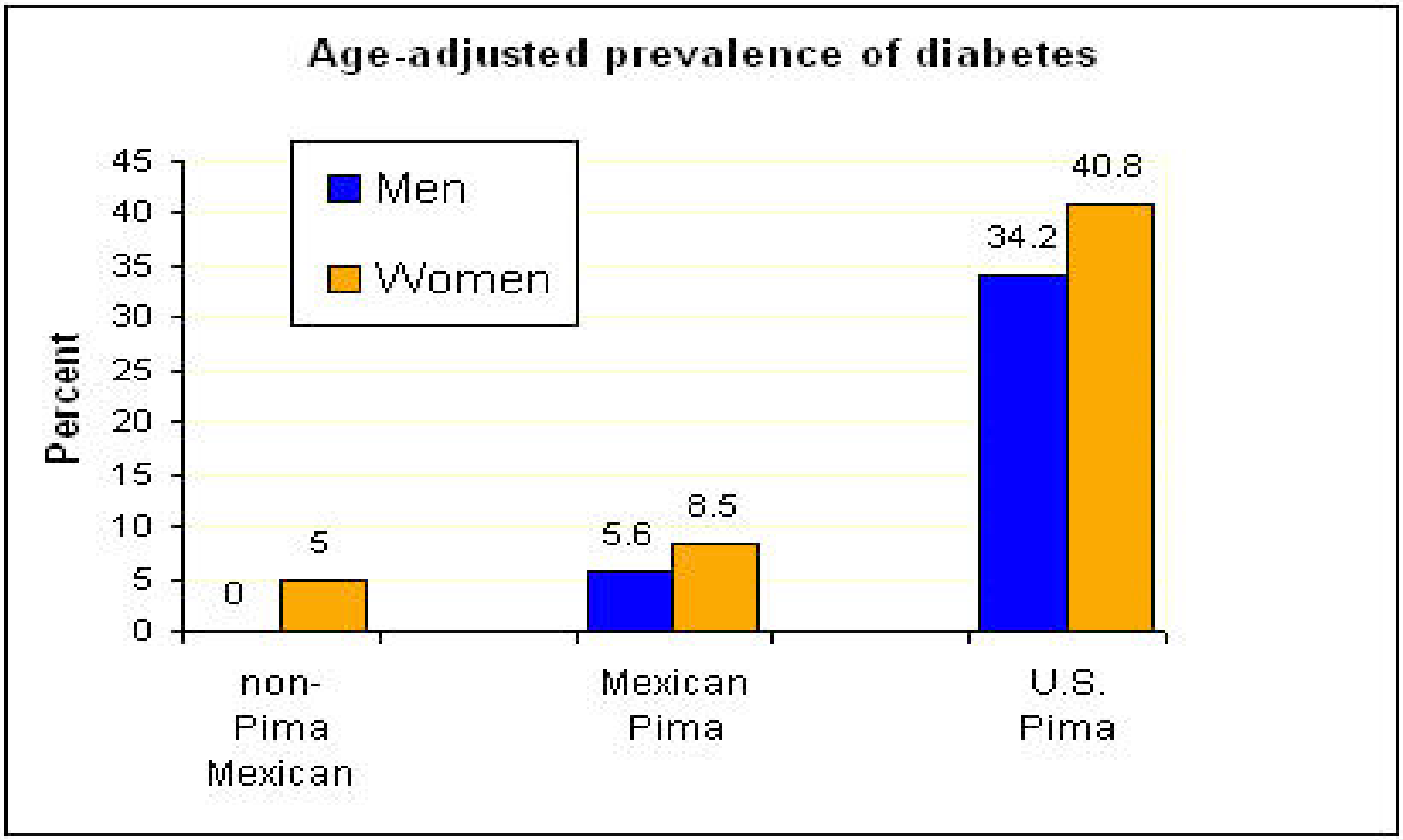


Source: For American Indians/Alaska Natives, the estimate of total prevalence was calculated using the estimate of diagnosed diabetes from the 2003 outpatient database of the Indian Health Service and the estimate of undiagnosed diabetes from the 1999–2002 National Health and Nutrition Examination Survey. For the other groups, 1999–2002 NHANES estimates of total prevalence (both diagnosed and undiagnosed diabetes) were projected to year 2005.

Pima Indians: A lesson in Population Genetics

Impact on Pima Society





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Diabetes in Kids

- one quarter to one third of children and teens are now overweight
- 8- to 10-year-olds represent the fastest-growing group of overweight and obese children
- Strong family history of diabetes with 45-80% have at least one parent with diabetes
- Typically from AA, Hispanic, PI, & Native Americans
- About 90% of children with type 2 have dark shiny patches on the skin
- Association with polycystic ovary syndrome (PCOS)

Acanthosis Nigricans

Back to….The DISEASE

“ HHS and DKA should be viewed as a similar disease process with the fundamental difference being in the metabolism of lipids during a period of relative insulin deficiency.”

Kitabchi et al. *2008 Standards of Medical Care in Diabetes* Diabetes Care January 2008

Remember the fundamentals

Type 1 DM

a cell mediated autoimmune or other destructive process of the pancreatic b-islet cells resulting in an absolute deficiency of insulin

Type 2 DM

insulin resistance

in a milieu of normal or increased levels of circulating insulin

Avoid: "IDDM & NIDDM"

Diabetes Variants

(Is there an endocrinologist in the room?)

- **Maturity Onset Diabetes (MODY)**
  - **6 genetic variants**
- **Late-onset Autoimmune Diabetes of Adulthood (LADA)**
  - **aka Slow Onset Type 1 diabetes**
  - **Type 1.5 diabetes.**

LADA: DM Type 1.5

- Often misdiagnosed as type 2
- Unlikely to run in family
- Non insulin resistance
- Insulin preferred to orals
- Positive AB's that attack B-cells

  GAD 65 (glutamic acid decarboxylase)

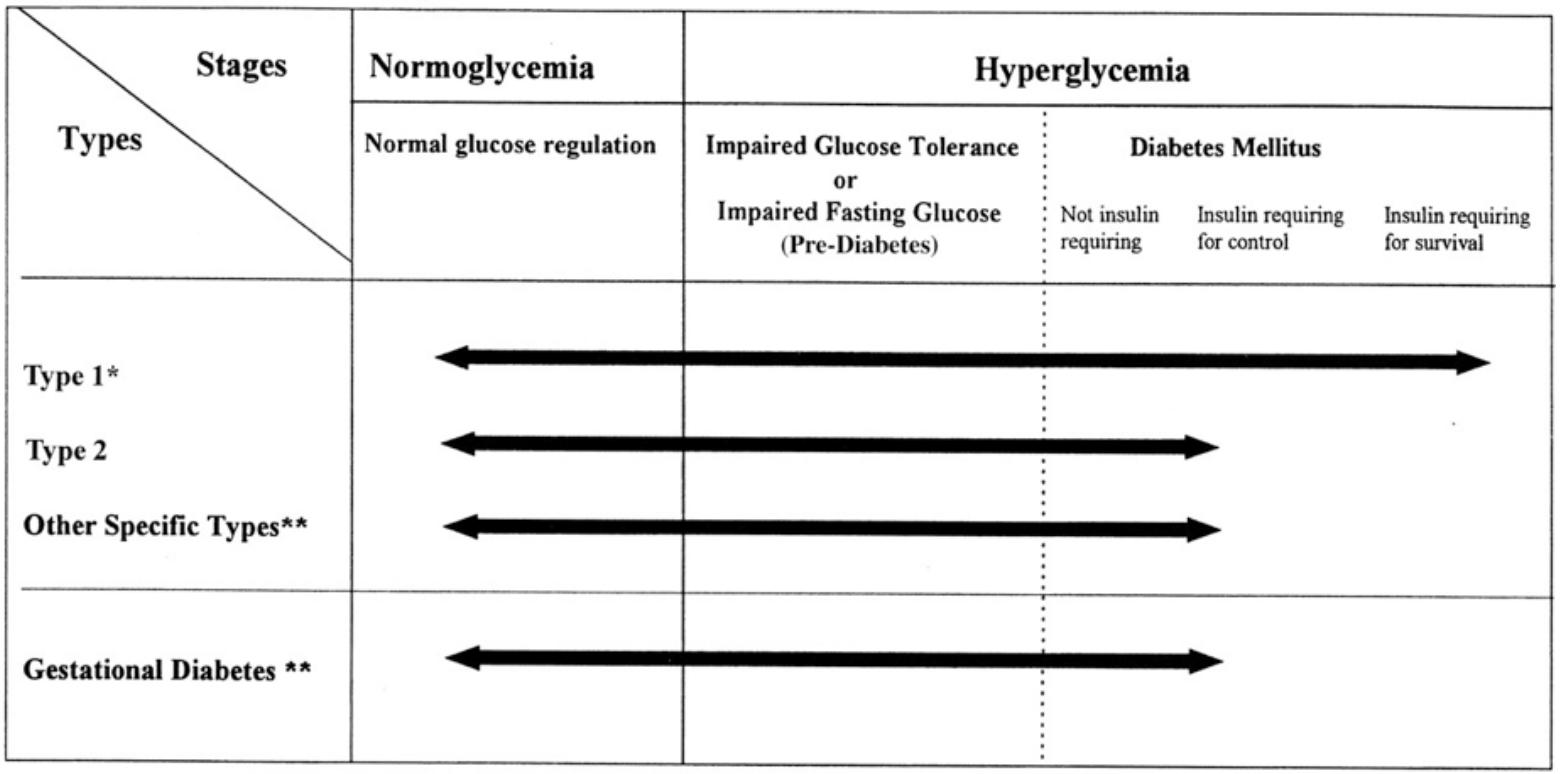
MODY: Maturity Onset Diabetes of Youth

- May make up as many as 5% of presumed type 1 and type 2 diabetes
- Time of onset 65% by age 25 100% by age 50
- Commonly expressed @ gestation
- Due to ineffective insulin production or release due to a gene mutation
- Autosomal dominant with FH of DM
- 6 different genotypes described
- Usually less resistance to glycemic control requiring smaller insulin doses

The long list…

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
  A. Immune mediated
  B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III. Other specific types
  A. Genetic defects of β-cell function
    1. Chromosome 12, HNF-1α (MODY3)
    2. Chromosome 7, glucokinase (MODY2)
    3. Chromosome 20, HNF-4α (MODY1)
    4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
    5. Chromosome 17, HNF-1β (MODY5)
    6. Chromosome 2, *NeuroD1* (MODY6)
    7. Mitochondrial DNA
    8. Others
  B. Genetic defects in insulin action
    1. Type A insulin resistance
    2. Leprechaunism
    3. Rabson-Mendenhall syndrome
    4. Lipoatrophic diabetes
    5. Others
  C. Diseases of the exocrine pancreas
    1. Pancreatitis
    2. Trauma/pancreatectomy
    3. Neoplasia
    4. Cystic fibrosis
    5. Hemochromatosis
    6. Fibrocalculous pancreatopathy
    7. Others
  D. Endocrinopathies
    1. Acromegaly
    2. Cushing's syndrome
    3. Glucagonoma
    4. Pheochromocytoma
    5. Hyperthyroidism
    6. Somatostatinoma
    7. Aldosteronoma
    8. Others
  E. Drug- or chemical-induced
    1. Vacor
    2. Pentamidine
    3. Nicotinic acid
    4. Glucocorticoids
    5. Thyroid hormone
    6. Diazoxide
    7. β-adrenergic agonists
    8. Thiazides
    9. Dilantin
    10. α-Interferon
    11. Others
  F. Infections
    1. Congenital rubella
    2. Cytomegalovirus
    3. Others
  G. Uncommon forms of immune-mediated diabetes
    1. "Stiff-man" syndrome
    2. Anti–insulin receptor antibodies
    3. Others
  H. Other genetic syndromes sometimes associated with diabetes
    1. Down's syndrome
    2. Klinefelter's syndrome
    3. Turner's syndrome
    4. Wolfram's syndrome
    5. Friedreich's ataxia
    6. Huntington's chorea
    7. Laurence-Moon-Biedl syndrome
    8. Myotonic dystrophy
    9. Porphyria
    10. Prader-Willi syndrome
    11. Others
IV. Gestational diabetes mellitus (GDM)

Disorders of glycemia: A continum



HHS & DKA: Notable Differences The LAB

	Diabetic ketoacidosis			
	Mild	Moderate	Severe	Hyperglycemic hyperosmolar syndrome
Diagnostic criteria and classification				
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–<7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10–<15	<10	>15
Urine ketone [a]	Positive	Positive	Positive	Small
Serum ketone [a]	Positive	Positive	Positive	Small
Effective serum osmolality [b]	Variable	Variable	Variable	>320
Anion gap [c]	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Variable
Typical deficits				
Total water (L)	6			9
Water (mL/kg) [d]	100			100–200
Na+ (mEq/kg)	7–10			5–13
Cl- (mEq/kg)	3–5			5–15
K+ (mEq/kg)	3–5			4–6
PO4 (mmol/kg)	5–7			3–7
Mg++ (mEq/kg)	1–2			1–2
Ca++ (mEq/kg)	1–2			1–2

The ADA
So…who's a diabetic?

FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

OR

Symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

OR

2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

Who's *almost* a diabetic: Glucose Intolerance

- Pre-dates onset of DM often by years
- Clinically inapparent
- Random glucose >160 mg/dl
- Fasting > 110 or <126 mg/dl
- Estimated 13.5 million Americans
- Average time to diagnosis of DM?

Who should be screened…

- Age > 45 then q 3 yrs
- BMI>25 plus
  - First-degree relatives
  - Non-caucasion
  - Couch potatoes
  - Women with GDM or big babies
  - HTN & lipids
  - <20 y/o acct. for 45% of all new cases of DM

Table 4—*Testing for type 2 diabetes in asymptomatic children*

Criteria
• Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors:
• Family history of type 2 diabetes in first- or second-degree relative
• Race/ethnicity (e.g., Native American, African American, Latino, Asian American, and Pacific Islander)
• Signs of insulin resistance or conditions associated with insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, or PCOS)
• Maternal history of diabetes or GDM
Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency: every 2 years
Test: FPG preferred

Clinical Scenario

- 77 y/o recent NHP recent d/c from hospital with CVA and right hemiparesis. EMS called to scene for AMS. On arrival patient is noted to be arousable but lethargic
- Patient c/c weak all over, “tired”
- PMHX: HTN, CVA, COPD, mild dementia
- Temp: Warm, P:54, R 50 BP 90/60
- Exam: dry MM, COR:S1S2, Lungs: CTA, Abd: Soft, mild suprapubic tenderness,
- LABS: Accucheck HHH
- Concerns?

QUESTIONS

What are your major concerns?

How did this little old lady get into trouble?

QUESTION

Why isn't HHS presenting as a more common complaint among the

16 million un-diagnosed

Type 2 diabetics ?

Access to…H_20

So who gets sick ?

So who gets HHS ?

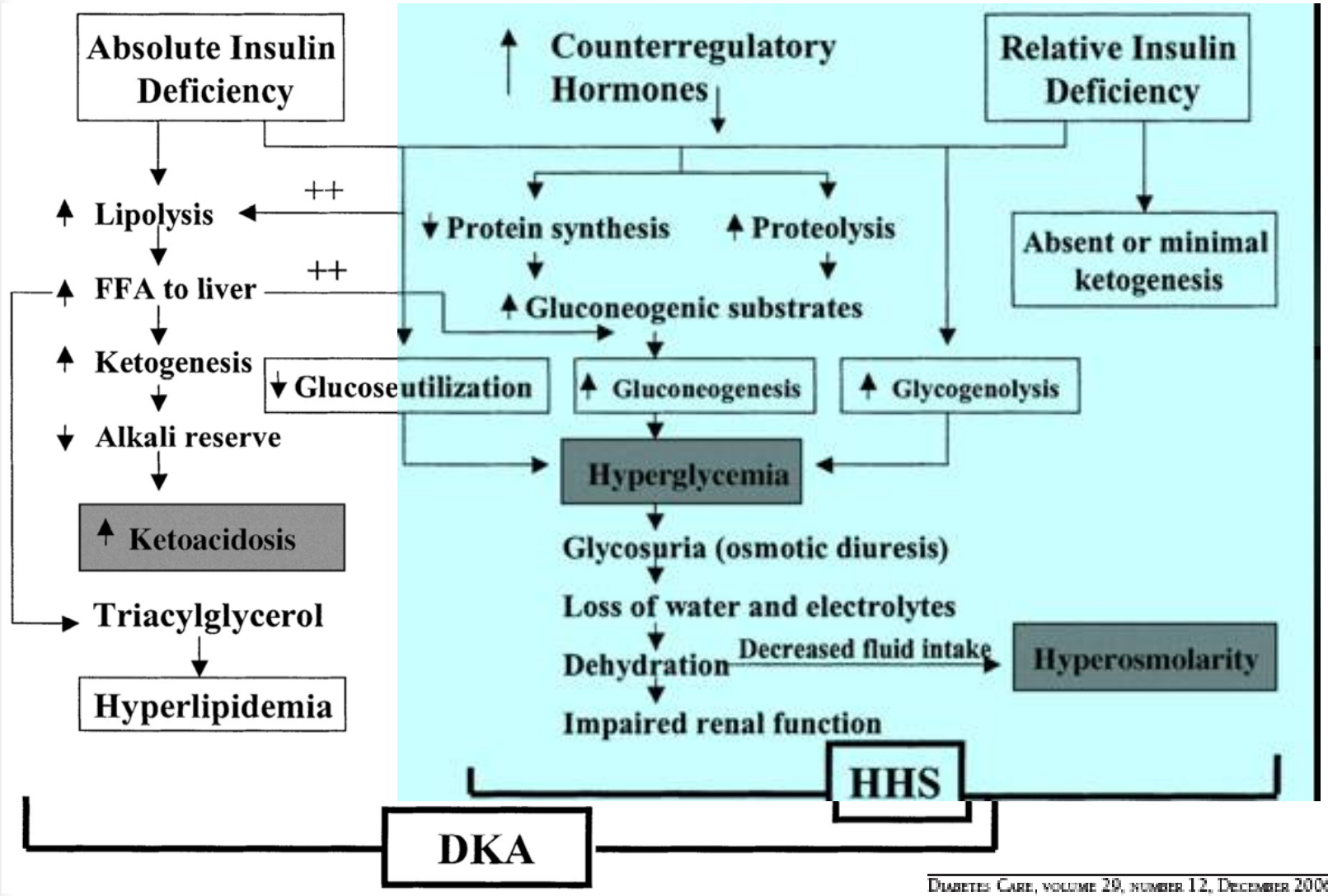
ELDERLY & INCAPACITATED

- Who need others to gain access to H20
- Who are unlikely to self refer
- Who typically feel bad much of the time anyway
- Who are on multi-pharmacy
- Have significant co-morbidities

So what happens in HHS…?

- An inciting event
- A reduction in response to insulin
- An elevation of counter-regulatory "stress" hormones
  (glucagon, catecholamines, cortisol, and GH)
- An osmotic diuresis with >GFR
- Dehydration and < GFR

In other words…



Diabetes Care, volume 29, number 12, December 2006

Essential differences:

	DKA			
	Mild	Modera	Severe	HHS
Plasma glucose (mg/dl)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.2	<7.00	>7.30
Serum bicarbonate (mEq/l)	15–18	10 to <1	<10	>15
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)†	Variable	Variable	Variable	>320
Anion gap‡	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/dro	Stupor/coma	Stupor/coma

*Nitroprusside reaction method; †calculation: 2[measured Na (ml
$(Na^+) - (Cl^- + HCO_3^-)$ (mEq/l). See text for details.

Relative mortality

DKA -> 2.5 - 10%

HHS -> 20 - 50%

Pinnes et.al. (Diab care 2006) Described 132 pts. HHS

- Mean age 75
- 84% precipitating factor
- 100% dehydration
- 8% had coma
- Mean glucose 407
- Mean Osm 380
- Mortality 20%

What else predisposes to HHS?

- Infection #1
- UTI
- Pneumonia
- Uremia
- Glucose intolerant
- Parenteral nutrition
- Pancreatitis
- Heat related illness
- MI
- CVA
- Rhabdomyolysis
- Mesenteric ischemia
- GI bleed
- Burns
- Peritoneal dialysis

Drugs: *Which are the two worst*

- **Diuretics**
- **ß-blockers**
- **Steroids**
- **Neuroleptics**
- **Benzo's**
- **Lithium**
- **Mannitol**
- **Dilantin**
- **Statins**
- **Ace Inhib.**

Drugs & HHS

- **Diuretics**
- **ß-blockers**
- **Steroids**
- **Neuroleptics**
- **Benzo's**
- **Lithium**
- **Mannitol**
- **Dilantin**
- **Statins**
- **Ace Inhib.**

Despite the etiology…remember

“ HHS and DKA should be viewed as a similar disease process with the fundamental difference being in the metabolism of lipids during a period of relative insulin deficiency.”

Kitabchi et al. *2008 Standards of Medical Care in Diabetes* Diabetes Care January 2008

Typical Pre-hospital history

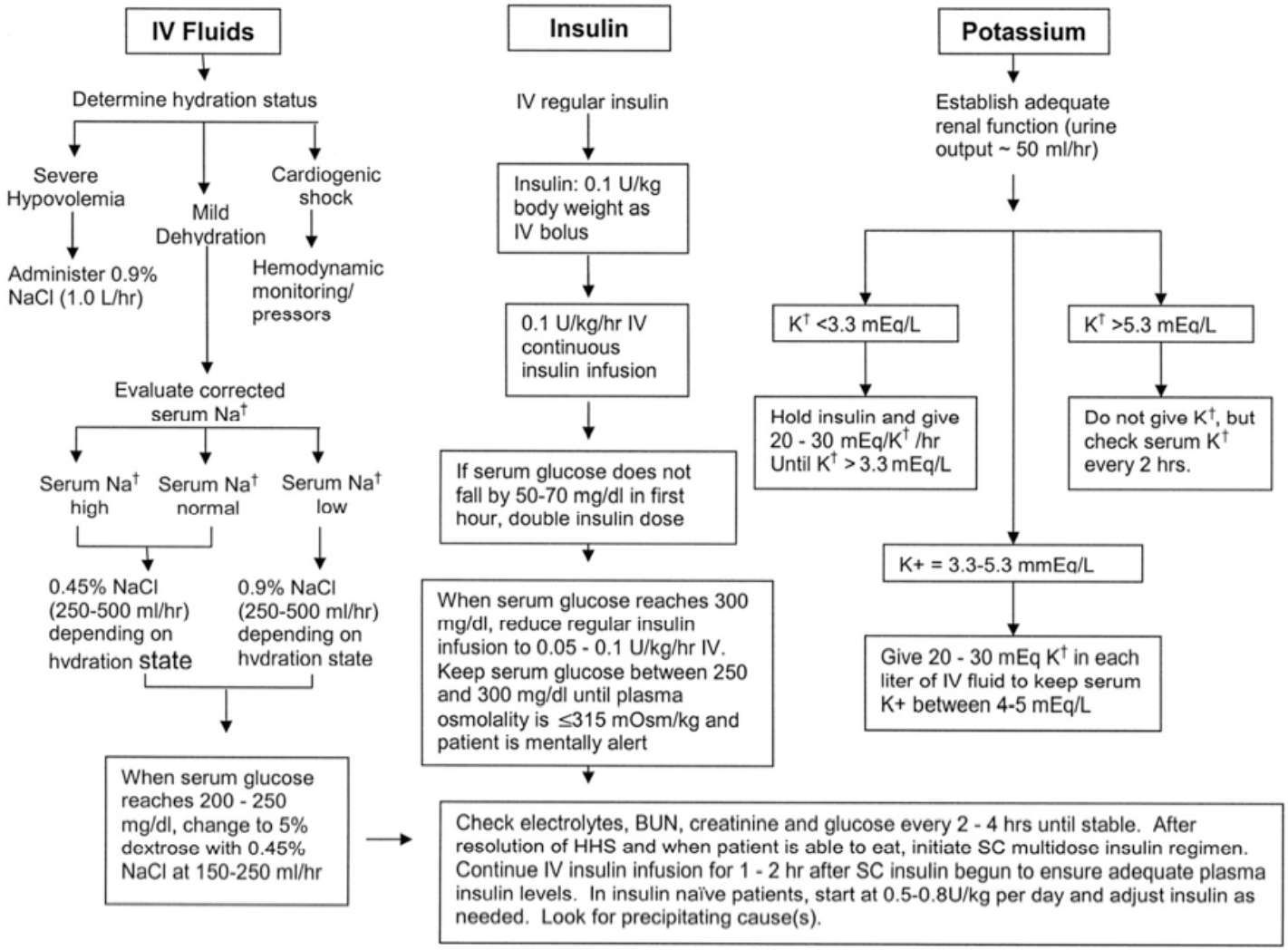
NHP 1 week after lab draw "WOW…check out these labs"

- **Change in mental status**
- **Acute febrile illness**
- **New onset seizure**
- **Hypotension**
- **Acute CVA**

The Exam

- Subtle changes in MS
- Search for precipitating problem
- Signs of profound dehydration
- 15% new onset seizure (focal)
- Hypothermia poorly prognostic
- Far along in the NH of disease

Approach to treatment…



Fundamentals of Treatment

- Correct hypovolemia first
- Rapid identification of precipitating causes
- Identify septic patient quickly
- Correct electrolyte abnormalities
- Antibiotics where indicated
- Strict attention to preexisting illness
- Avoid overzealous resuscitation
- Insulin therapy

Fluids….

Hydrate for first hour

Initial 0.9% NaCl 1-2 L

then 0.45% NaCl (eu or hypernatremic)

then D5 .45% NaCl (250-300mg/dl)

then PO

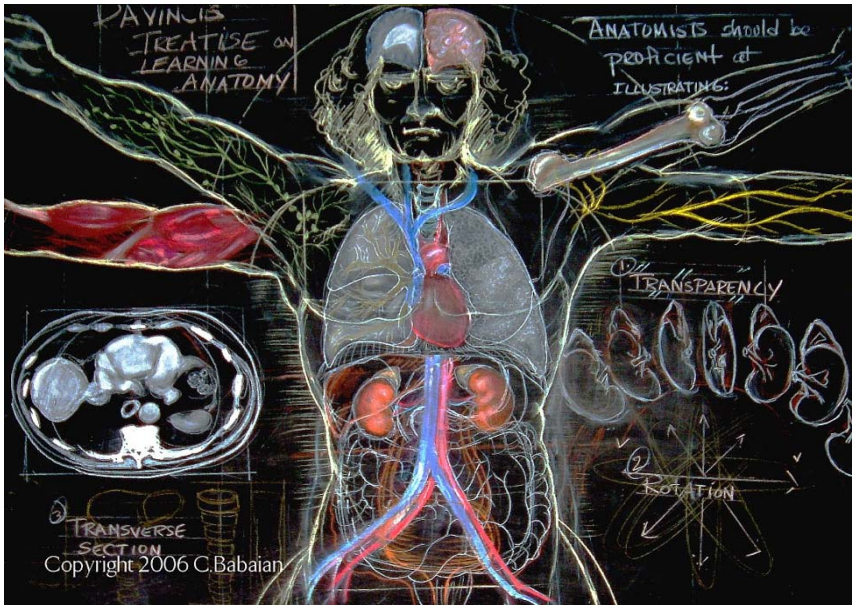
1/2 fluid deficit should be replaced first 12 hrs with remainder over subseq 24 hrs.

What can go *really* wrong? Cerebral Edema

- First described in 1933 (Dillon, Riggs & Dyer)
- Accounts for 70% of deaths in DKA in young patients
- Very rare in adults
- Early identification and frequent reassessments are critical
- Some studies demonstrate edema prior to initiation of treatment
- Sub-clinical cerebral edema may occur prior to institution of treatment
- 48 hr rehydration vs. 24 hr may offer theoretical protection

Complications

- CHF
- KCl derangements
- Cerebral Edema
- Failure to diagnose
- Hypoglycemia
- Early Consults



In Summary

- Avoid getting hung up on “type 1 or type 2”
- Early identification of precipitating problem
- Identify meds that could be contributing
- Avoid overzealous resuscitation
- Frequent serial exams assessing cognition
- Anticipate role of co-morbid issues
- Remember sepsis
- Appropriate Goal Directed Therapy

Thanks!