"Dare to Dream: A Future Without Lows"

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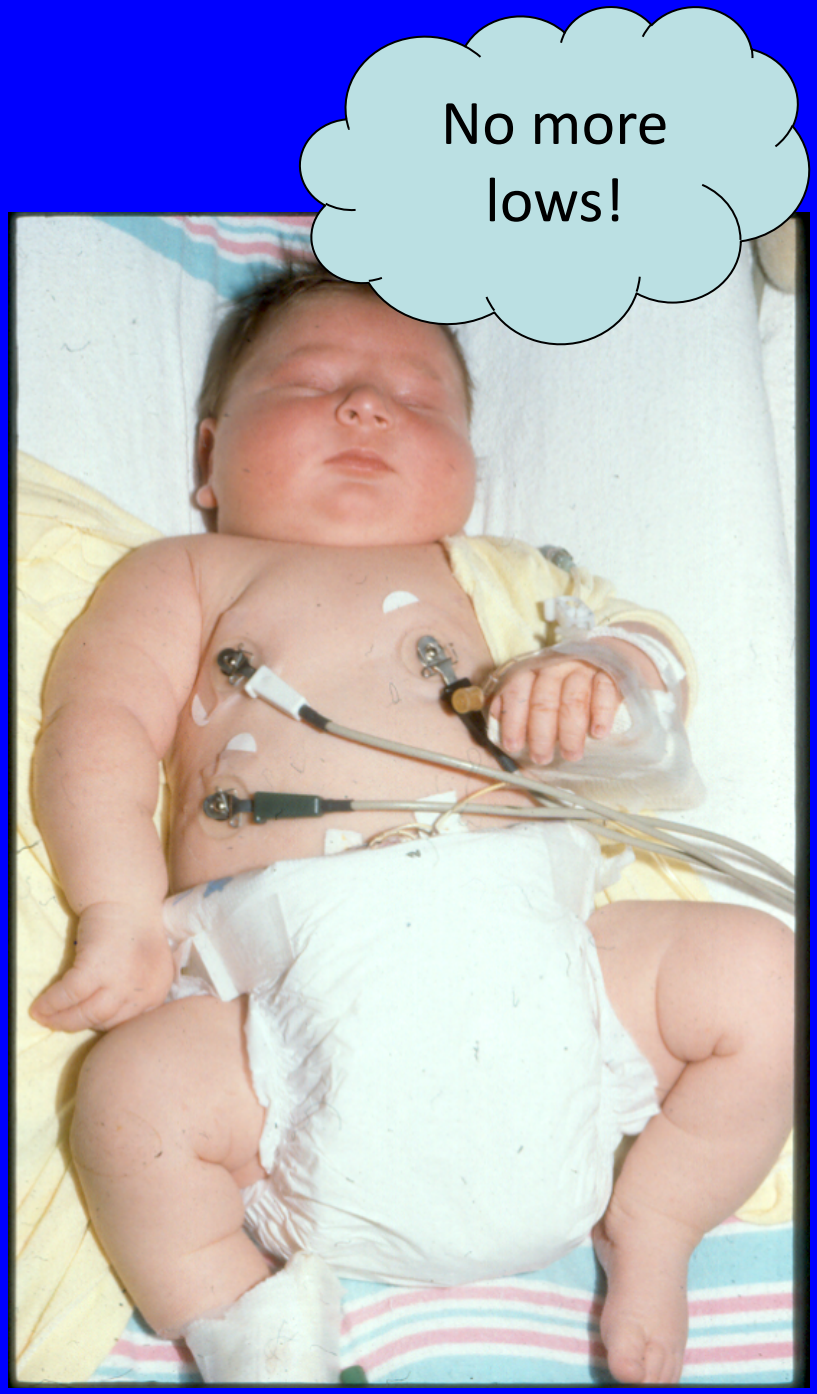
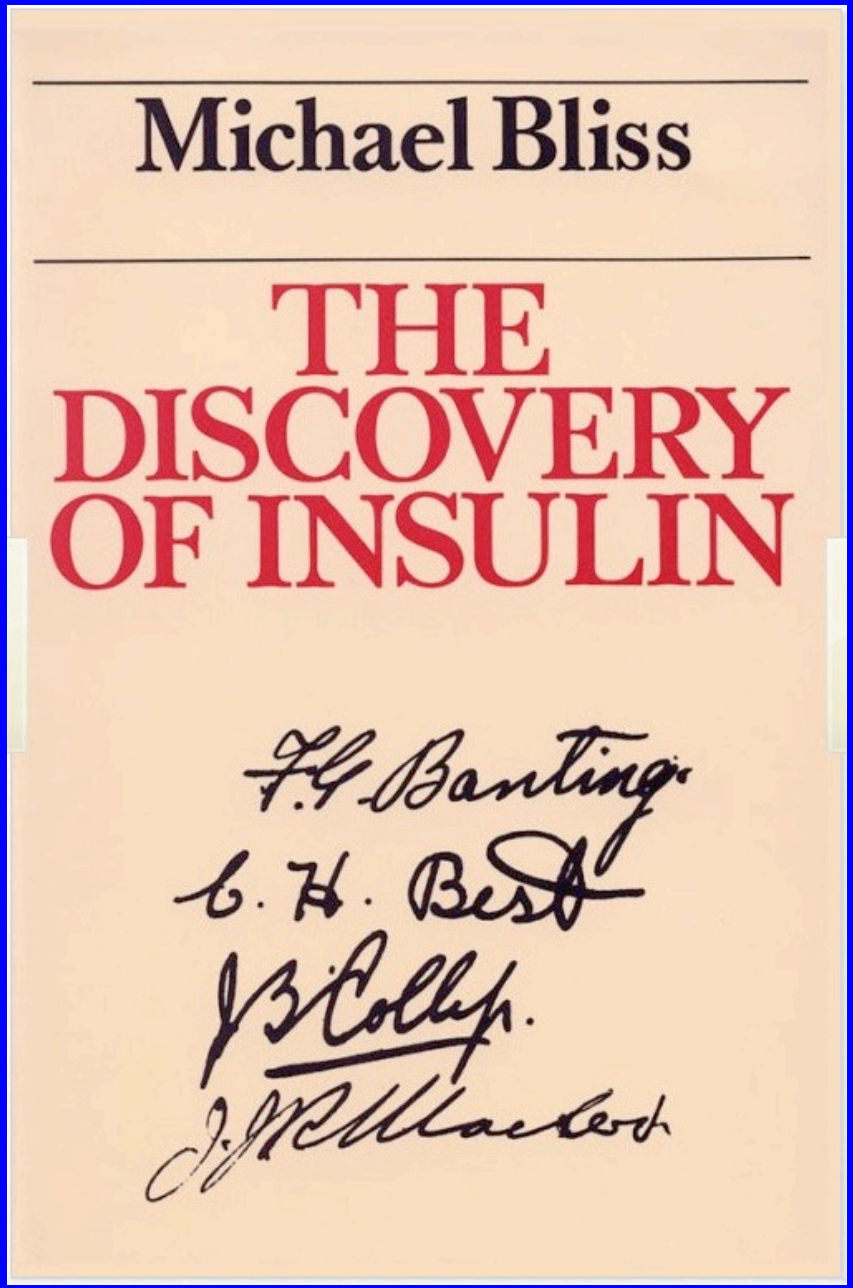
CHOP



100 years ago

Discovery of Hypoglycemia January, 1922

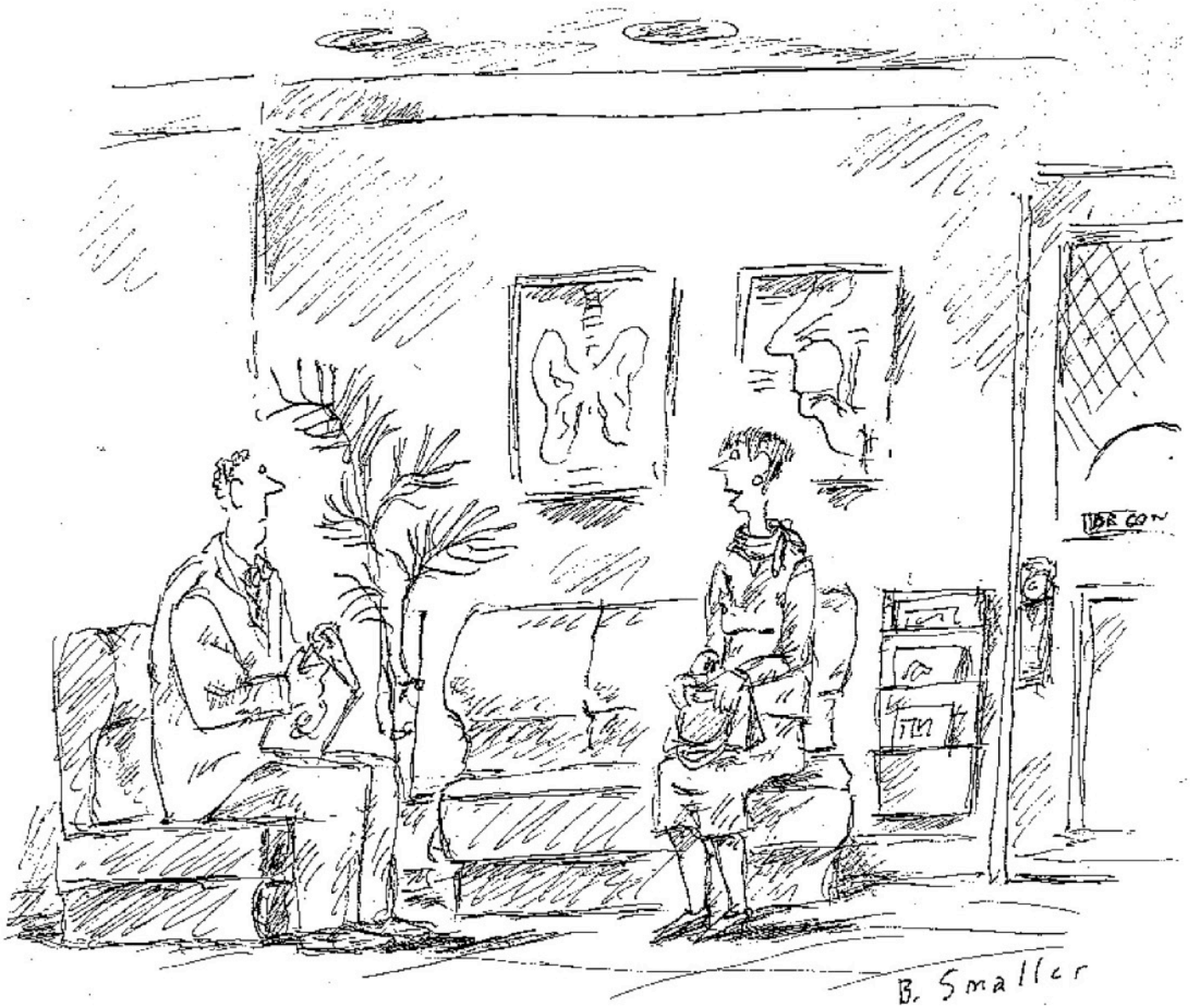
Insulin-treated diabetic has first recognized hypoglycemic event



Dreaming of a Future Without Lows

- Where did we start?
- Where are we?
- Where can we go?

Where can we go?



"It's a very rare disease—it doesn't have a cure.
It doesn't even have a spokesperson."

Where can we go?

Dreaming of a Future Without Lows

Dream 1: Universal enrollment in CHI Global Registry

1) Unified voice for ALL types of HI (including perinatal-stress HI)

2) Amplify the voice of ”orphan” types of HI (e.g., HNF-HI, Kabuki Synd, PGM1-HI ….)

3) Define societal impact of HI: frequency, costs (medical, social, economic…), and current practices

4) Provide infrastructure for research (subjects for clinical trials, pilot grants, new treatment opportunities, outcomes research…)

Where did we begin?

”Idiopathic Hypoglycemia of Infancy” is a genetic disorder

High risk of “irreparable brain damage” caused by:

1) Delayed diagnosis

2) Inadequate (early) therapy

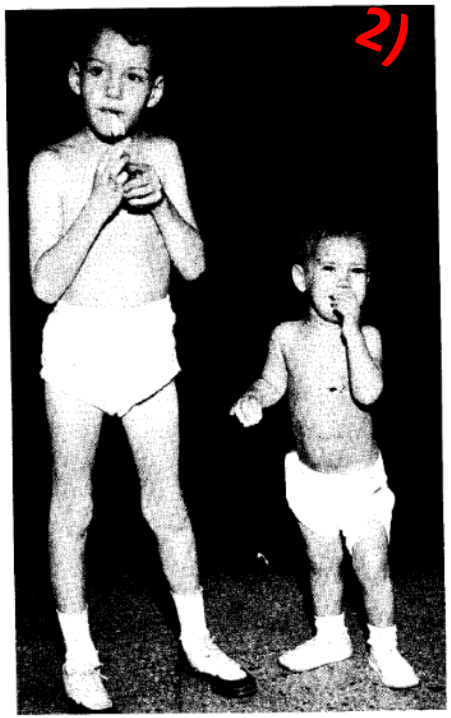


Fig. 3.—Photograph of J. G., aged 6 years, and B. G., aged 15 months. Taken two months after beginning of corticotropin therapy. Pancreatic resection scars visible.

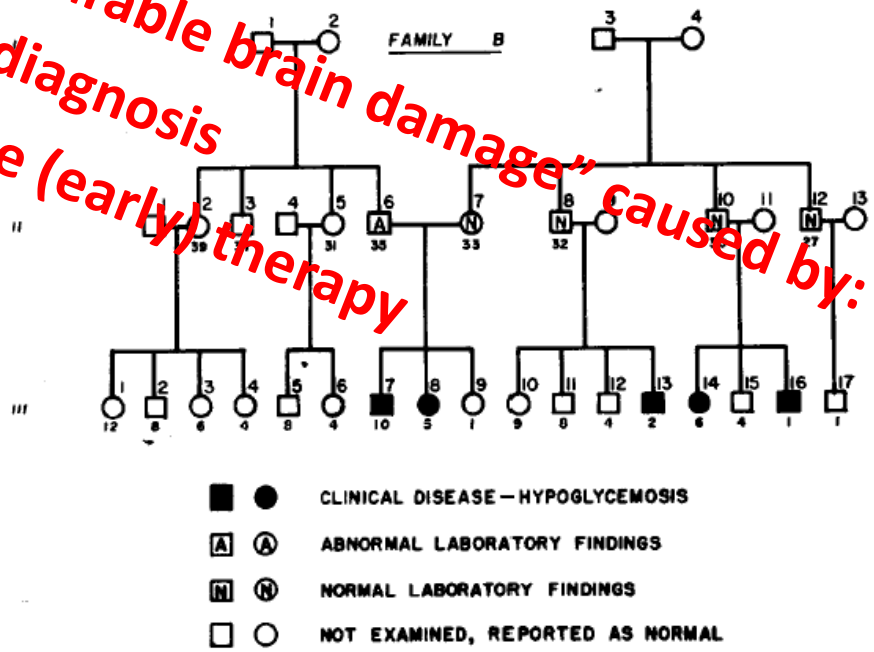


Fig. 2.—Genetic factor in the syndrome of idiopathic spontaneous hypoglycemia. Family A, pedigree of the R. family. Family B, pedigree of the W. family (J. G., B. G., J. W., and P. W.).

McQuarrie 1954

Dream 2: Universal Newborn Screening for HI

1) Difficult because ALL newborns have a mild form of HI until 1-2 days old

2) BUT, essential for early detection and prevention of "irreversible brain damage"

3) Possibilities:
   1) Find a unique marker for congenital / genetic HI (no ideas, but….)
   2) Combined monitoring of glucose and ketone levels for 2-3 days (captures both congenital HI and perinatal stress HI, but that's a good thing, anyway)
   3) ???

Screening for HI by monitoring glucose and ketones

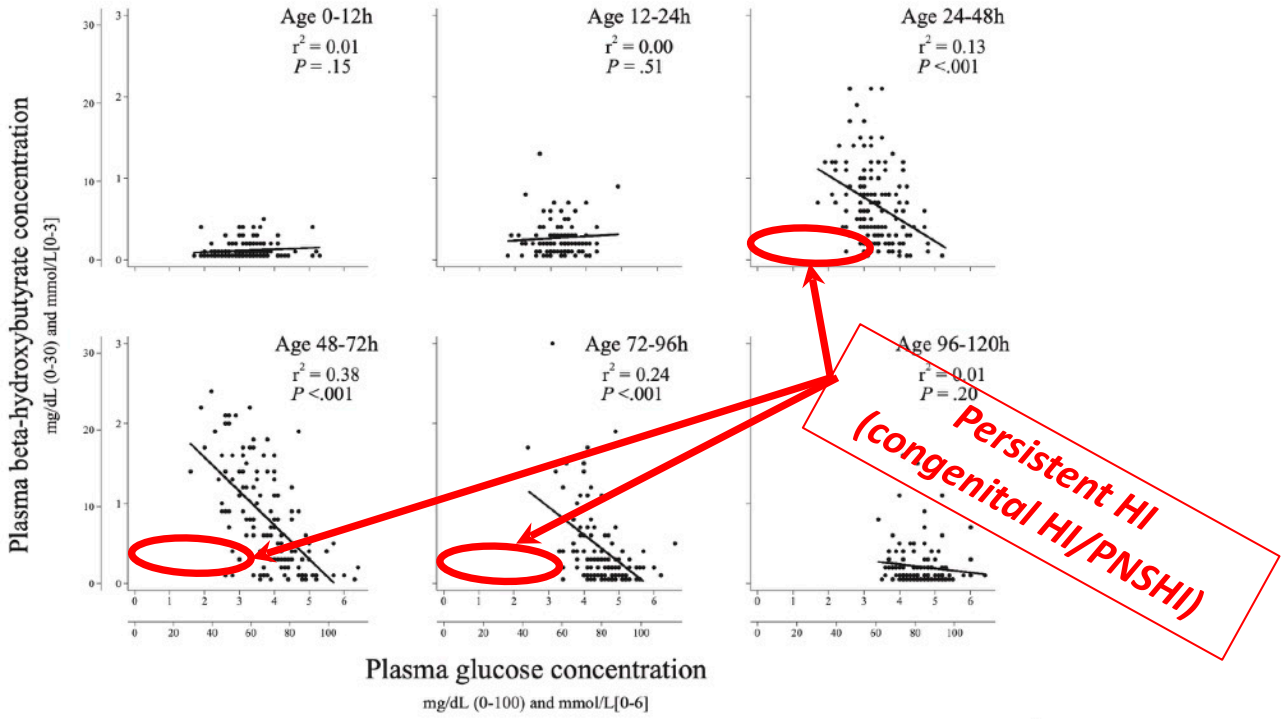


Figure 2. The relationship between plasma BHB and glucose concentrations at differing postnatal ages. The r^2 and P values are for simple linear regression analyses.

Alternative Cerebral Fuels in the First Five Days in Healthy Term Infants: The Glucose in Well Babies (GLOW) Study. Deborah L. Harris, PhD1,2,3, Philip J. Weston, MBChB1, and Jane E. Harding, DPhil2. *J Pediatr 2021;231:81-6*

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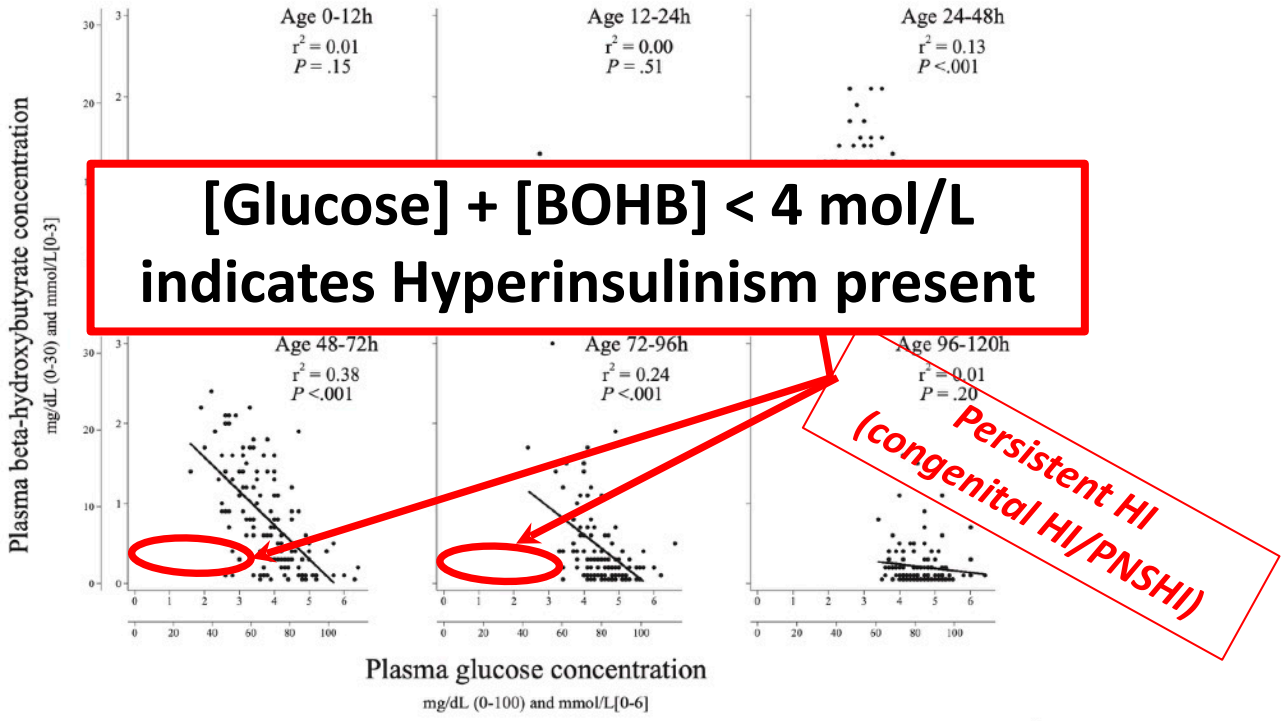

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Where can we go?

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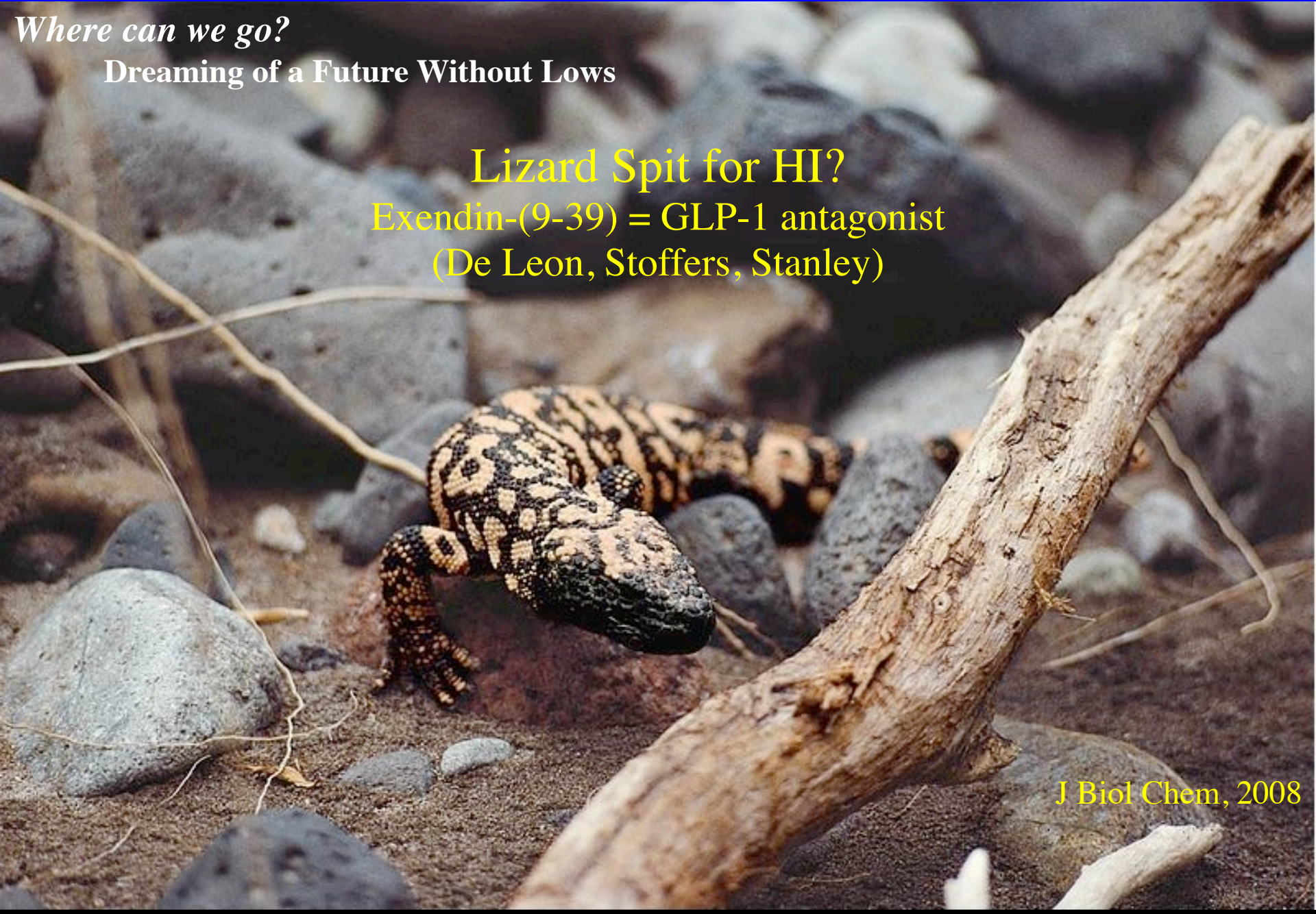

Lizard Spit for HI?

Exendin-(9-39) = GLP-1 antagonist

(De Leon, Stoffers, Stanley)

J Biol Chem, 2008

Dream 3: New and better treatments for HI

1) Current pipeline has >5 promising drugs (Rezolute, Crinetics, Eiger, Hanmi, Zealand, Nanjing Inst, …?)

2) Better monitoring: e.g., CGM sensors and glucose meters that are accurate at low glucose levels

3) Genetic engineering / cell therapy for cure of HI (?)

Where can we go?