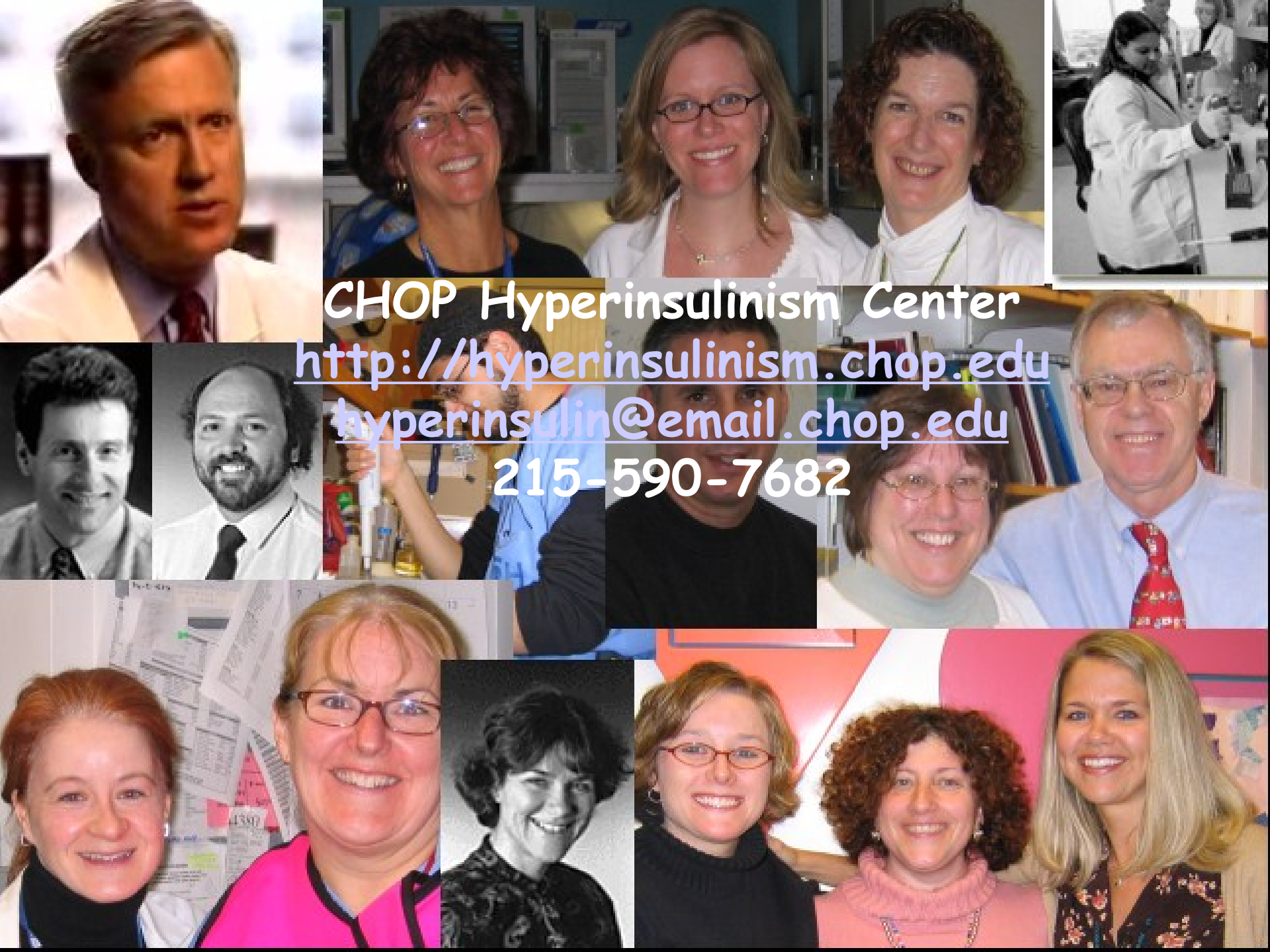
History of Congenital Hyperinsulinism: Treatment and Research

Charles A. Stanley, MD
Endocrinology Division
Children's Hospital of Philadelphia



CHOP Hyperinsulinism Center

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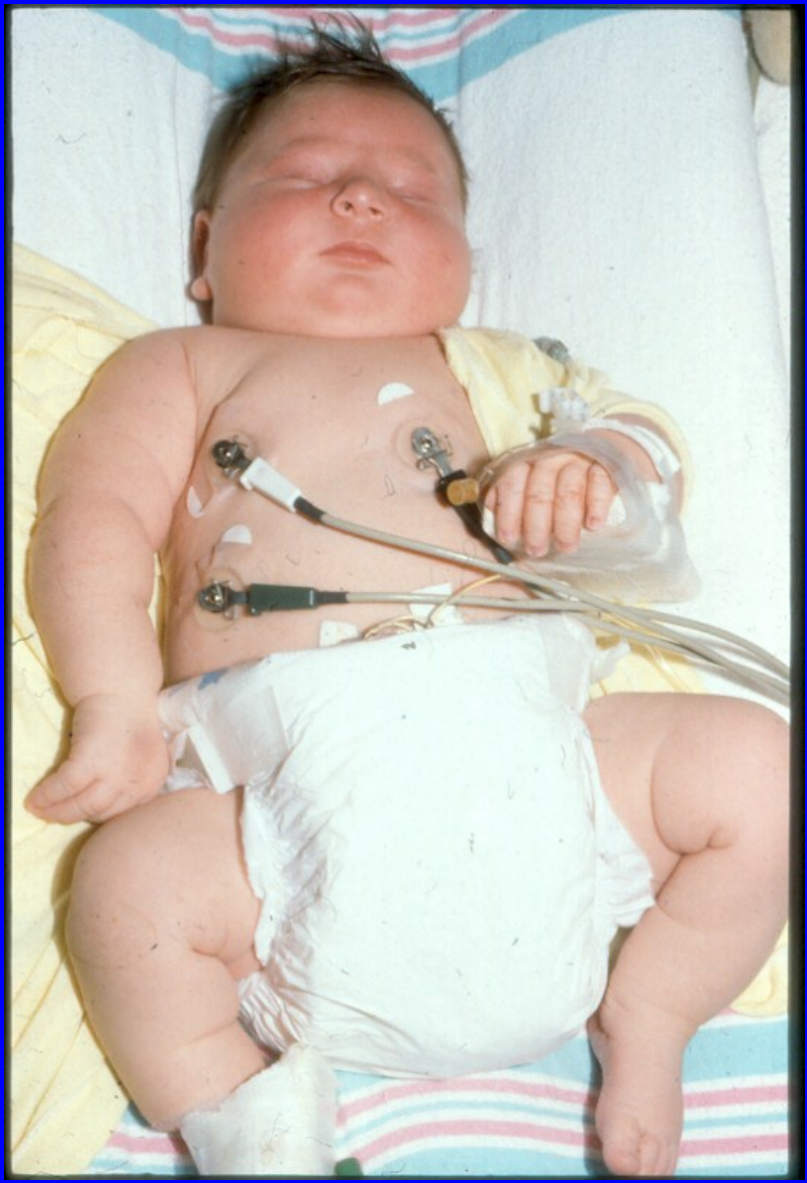
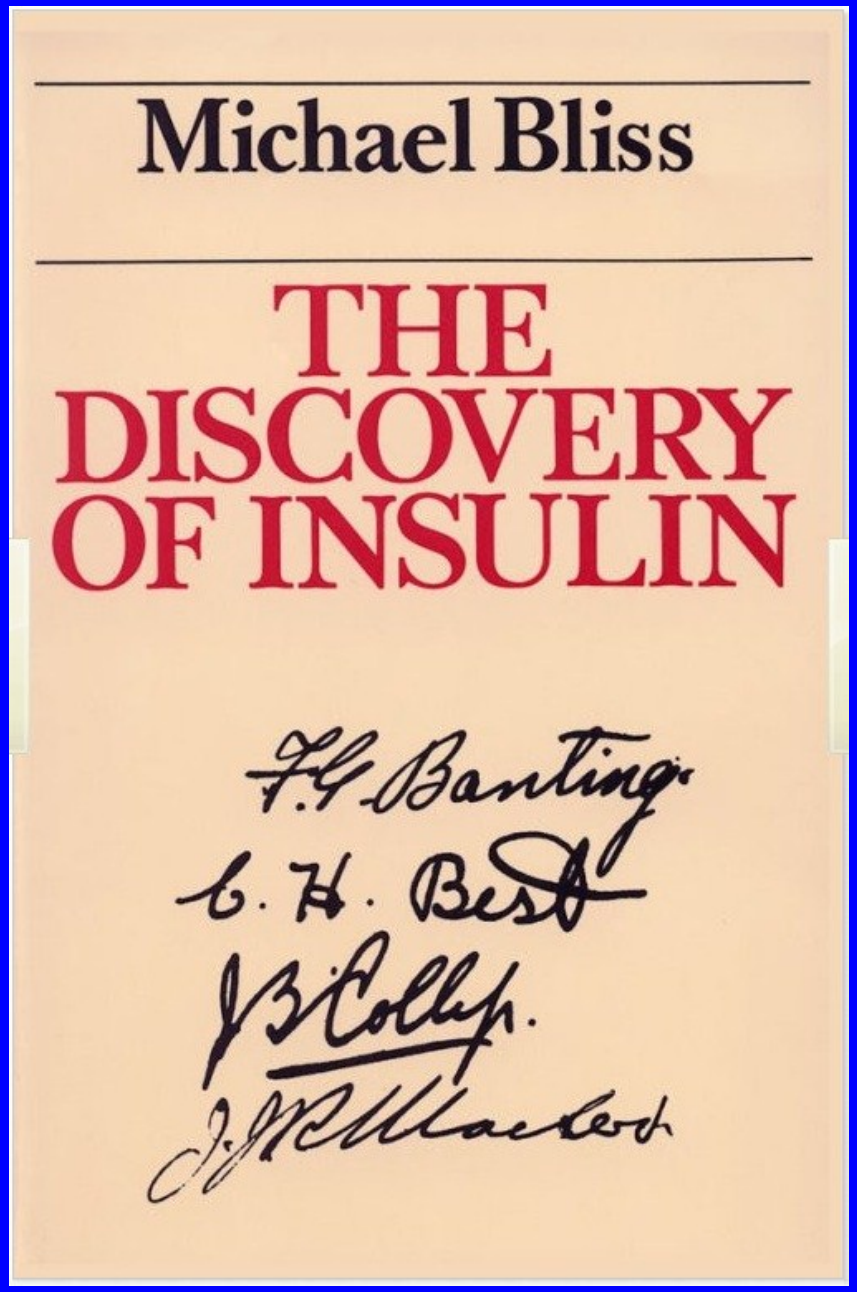
The Children's Hospital *of* Philadelphia®

CONGENITAL
HYPERINSULINISM CENTER



Discovery of Hypoglycemia
January, 1922
(? by J.B. Collip)



A. M. A.
American Journal of Diseases of Children
VOLUME 87 APRIL 1954 NUMBER 4

IDIOPATHIC SPONTANEOUSLY OCCURRING HYPOGLYCEMIA IN INFANTS

Clinical Significance of Problem and Treatment

IRVINE McQUARRIE, M.D.
MINNEAPOLIS

IN KEEPING with tradition concerning the choice of subject for a presidential address, I originally prepared a semiphilosophical dissertation for this occasion. Now, I must apologize to you for the sin of "deviation," because I suddenly decided only a few days ago to scrap that laboriously composed oration and substitute a résumé of some observations that my associates and I have made during the past few years in dealing with the clinical problem of spontaneous hypoglycemia in infants.

My seemingly impulsive decision to change to the latter title was the direct result of my seeing the seventh young child, among a series of cases recently examined in our clinic, who had suffered irreparable brain damage from severe hypoglycemia. Three of these were children who were victims of the misuse of insulin in the treatment of diabetes mellitus. The remaining four were examples of severe spontaneous hypoglycemia in infants who were victims of delayed diagnosis and inadequate early therapy.

The tragedy of permanent brain damage resulting from therapeutically induced hypoglycemia * is too well known and the precautions necessary for its avoidance are too obvious to justify special consideration at this time. The situation is quite different, however, in regard to the special group of infants with spontaneous hypoglycemia which I have felt compelled to discuss here today. There have been well-documented cases of brain damage associated with spontaneous hypoglycemia.†

Idiopathic Hypoglycemia: Concerns in 1953

1. Risk of irreparable brain damage
   a) Delayed diagnosis
   b) Inadequate (early) therapy

2. Cause?

3. Genetic?

4. Treatment?
   Pancreatectomy vs Cortisone

McQuarrie 1954

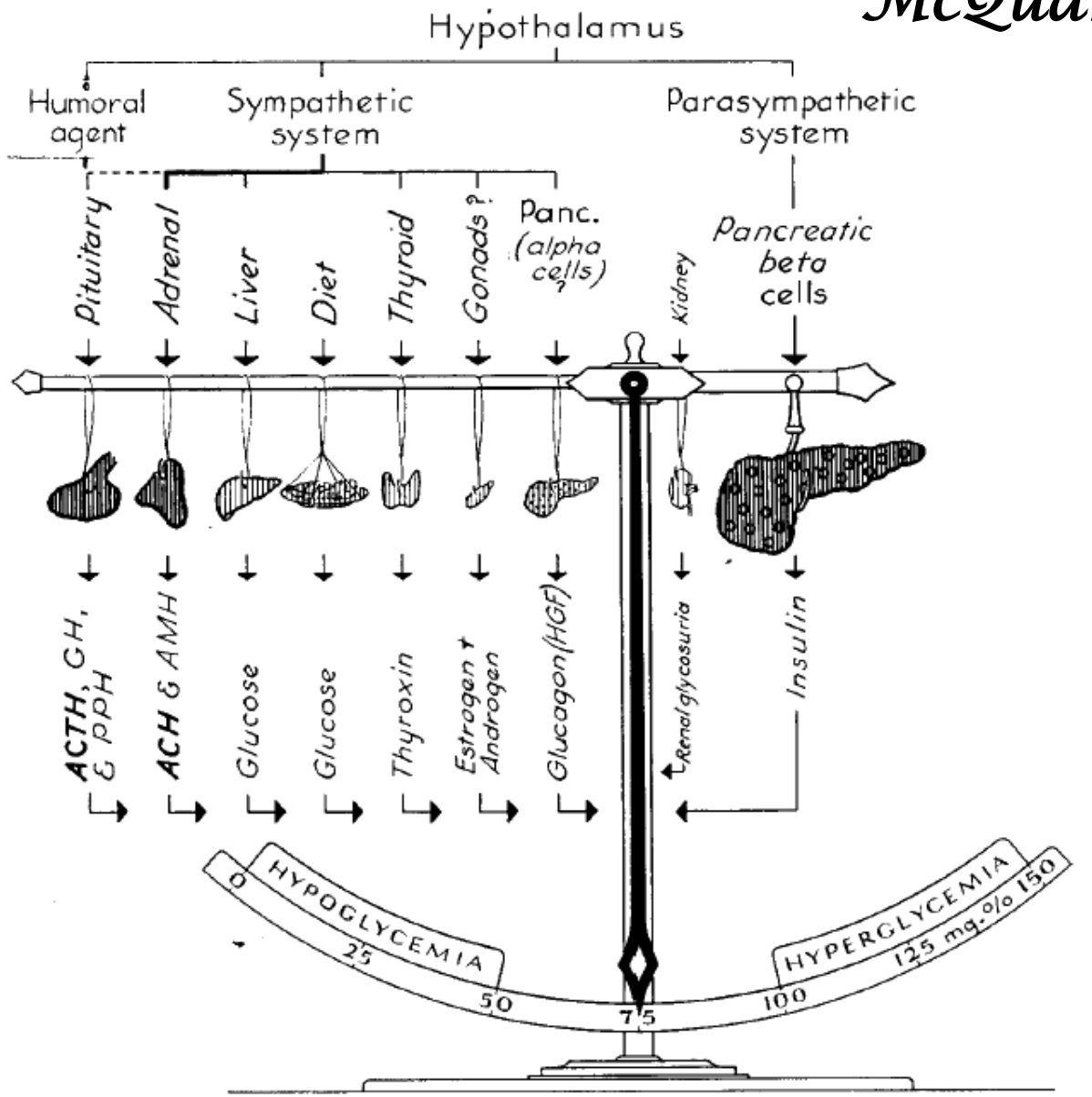


Fig. 1.—Schematic representation of balance between hypoglycemic and hyperglycemic factors affecting carbohydrate metabolism.

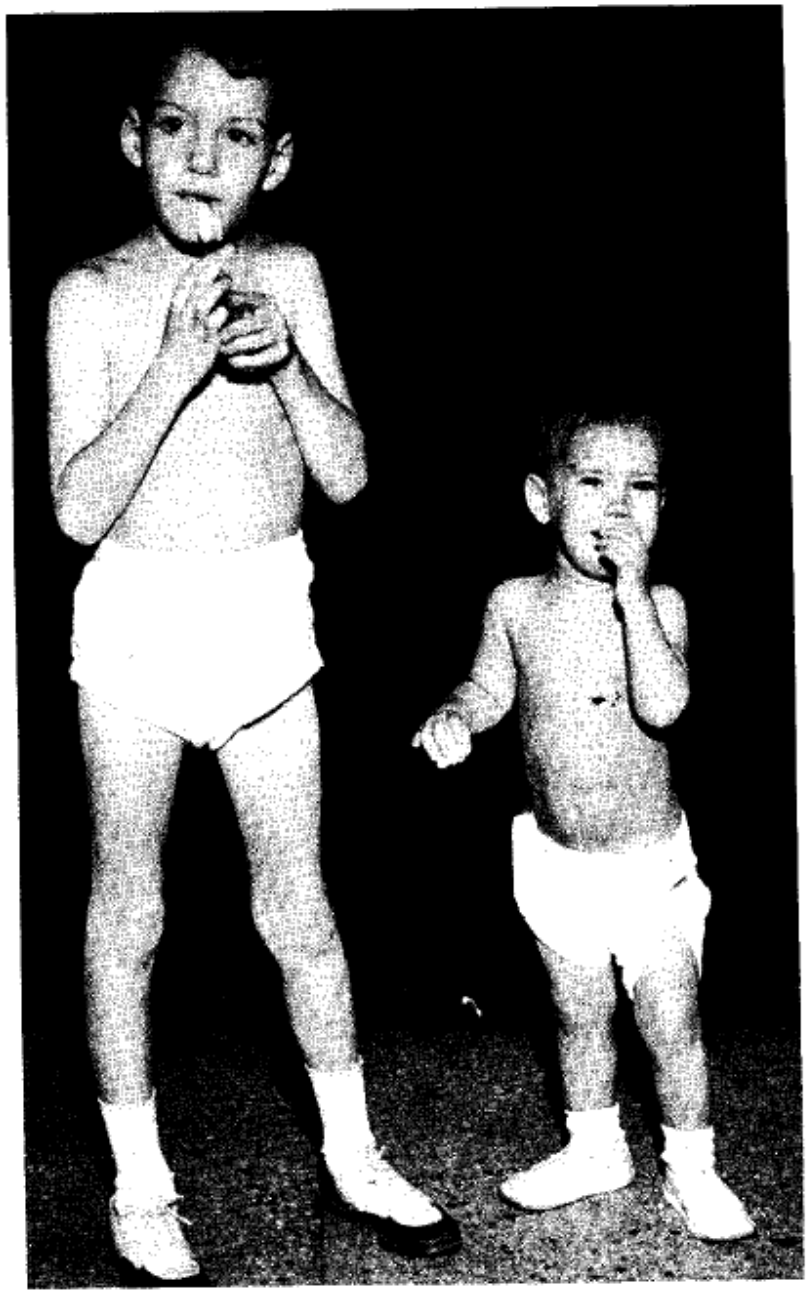


Fig. 3.—Photograph of J. G., aged 6 years, and B. G., aged 15 months. Taken two months after beginning of corticotropin therapy. Pancreatic resection scars visible.

McQuarrie 1954

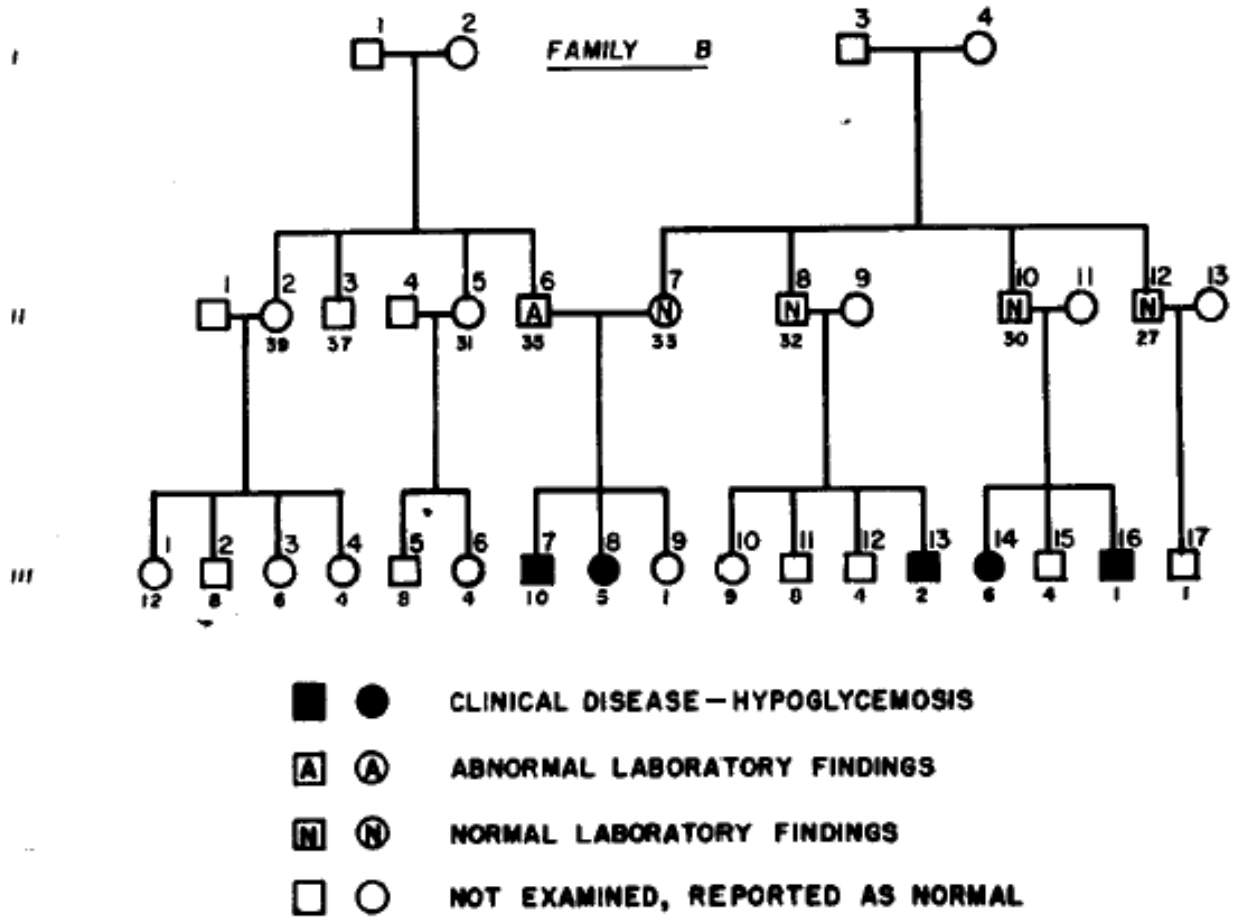


Fig. 2.—Genetic factor in the syndrome of idiopathic spontaneous hypoglycemia. Family A, pedigree of the R. family. Family B, pedigree of the W. family (J. G., B. G., J. W., and P. W.).

McQuarrie 1954

J Clin Invest 1955

FAMILIAL HYPOGLYCEMIA PRECIPITATED BY AMINO ACIDS

By W. A. COCHRANE,[1] W. W. PAYNE, M. J. SIMPKISS, and L. I. WOOLF

(*From the Hospital for Sick Children, Great Ormond Street, London, W. C. 1, England*)

(Submitted for publication September 13, 1955; accepted November 23, 1955)

Mann and Magath (1) in 1922 first described the clinical symptoms associated with hypoglycemia, and in 1924 Harris (2) reviewed its sub-

Hypoglycemia induced by protein feeding, especially leucine

individual cases and suggesting various surgical and medical methods of management.

Although spontaneous hypoglycemia is evidence of abnormal carbohydrate metabolism, this abnormality may be due to a variety of diseases.

The present communication describes three cases of hypoglycemia occurring in one family, and one unrelated case, in which convulsions and profound lowering of the blood glucose were induced by the administration of proteins or amino acids.

We believe this abnormal relationship between amino acids and glucose metabolism has not been previously described, and will be of great interest, not only to the clinician, but also to the biochemist and physiologist investigating carbohydrate and protein metabolism.

day—the fasting level being around 50 mg. per 100 ml. and by 10 p.m. the level had dropped to around 30 mg. per 100 ml.

A high protein low carbohydrate diet (cow's milk with added casein) was then given and she immediately began to have convulsions which occurred at about one hour after each feed. On "Soylac," a soya flour synthetic milk, she had numerous convulsions, her fasting blood sugar was only 20 mg. per 100 ml. and this tended to drop slightly during the day. She was then fed with expressed breast milk, the levels of blood sugar before feeds were higher and the baby was free from fits for the first time. Cow's milk diluted with three parts of water and with added sugar had the same effect. Mixed feeding was started, care being taken to see that no large amount of protein was given without carbohydrate being given at the same time. She has remained well, having about one fit every six weeks. Her mental and physical development are normal.

Case 2. A female infant, elder sister of case 1, was admitted to The Hospital for Sick Children, Great Ormond Street on 30th May 1953 at the age of 2½ months. Her birth weight was 7 lb. 1 oz. and her mother's pregnancy and labor were normal. She was breast fed for

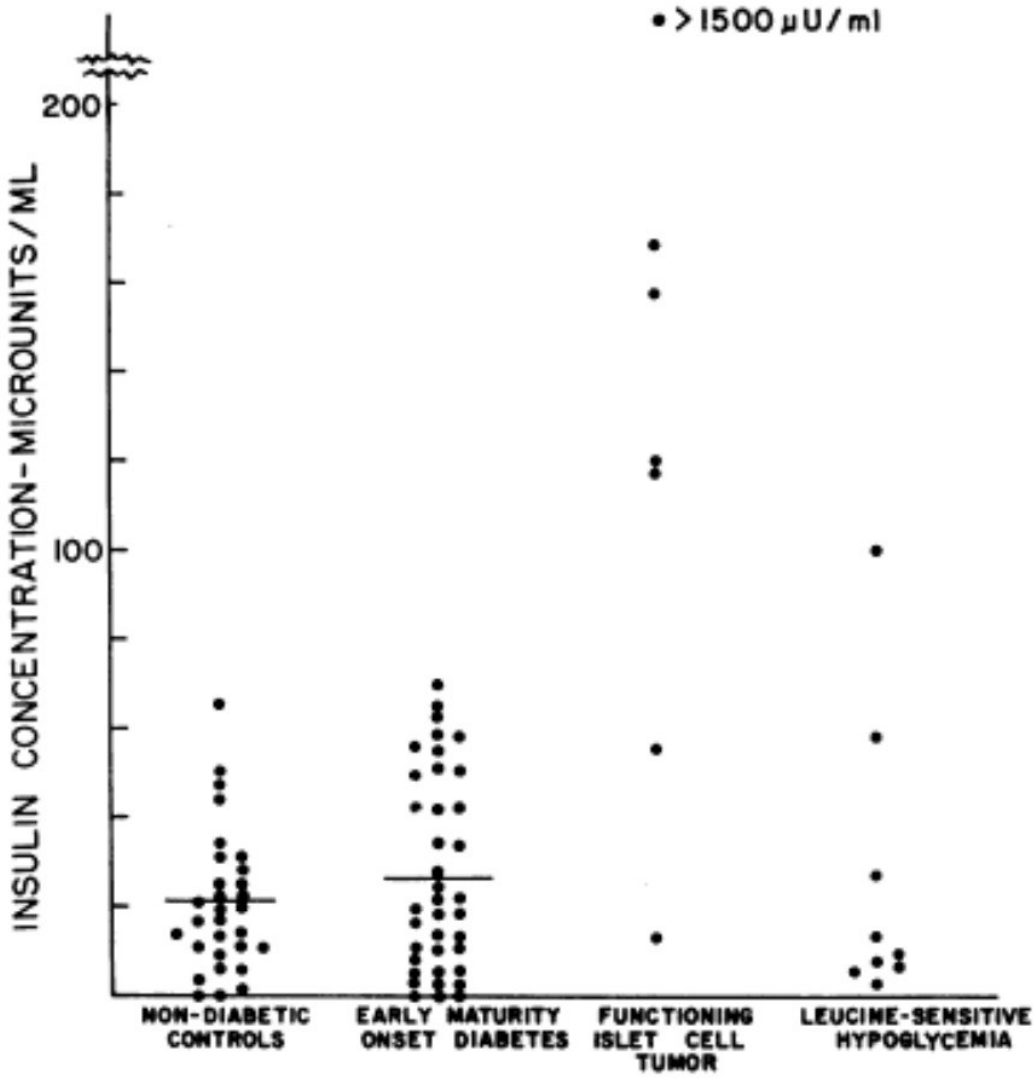


FIG. 8. FASTING PLASMA INSULIN CONCENTRATIONS IN VARIOUS GROUPS OF SUBJECTS. The subject with plasma insulin concentration greater than 1,500 μU per ml had an islet cell adenocarcinoma with widespread metastases (patient of Dr. J. Field).

Berson and Yalow *J. Clin. Invest.* (1960)

Hyperinsulinism in Infants and Children: Diagnosis and Therapy*

CHARLES A. STANLEY, M.D., AND
LESTER BAKER, M.D.

Division of Endocrinology, Children's Hospital of Philadelphia, and the Department of Pediatrics, University of Pennsylvania School of Medicine

Adv Pediatr 1976

Idiopathic Hypoglycemia (1953)

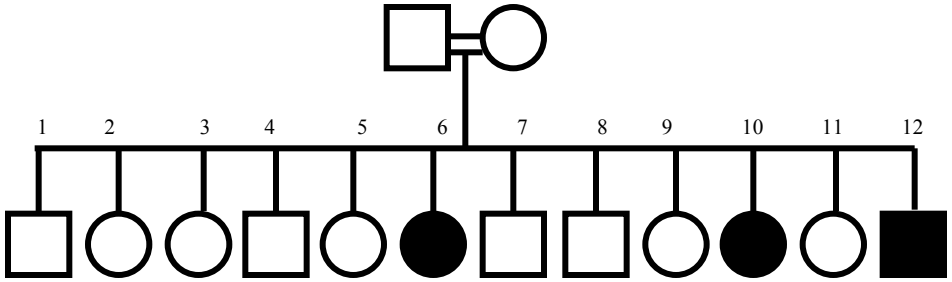
=

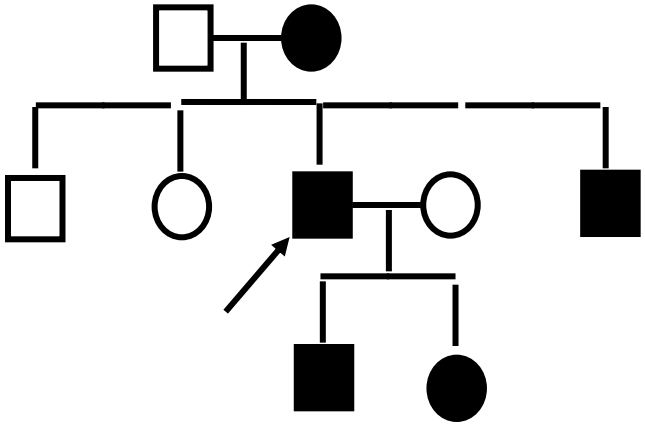
Congenital Hyperinsulinism (2009)

Synonyms:

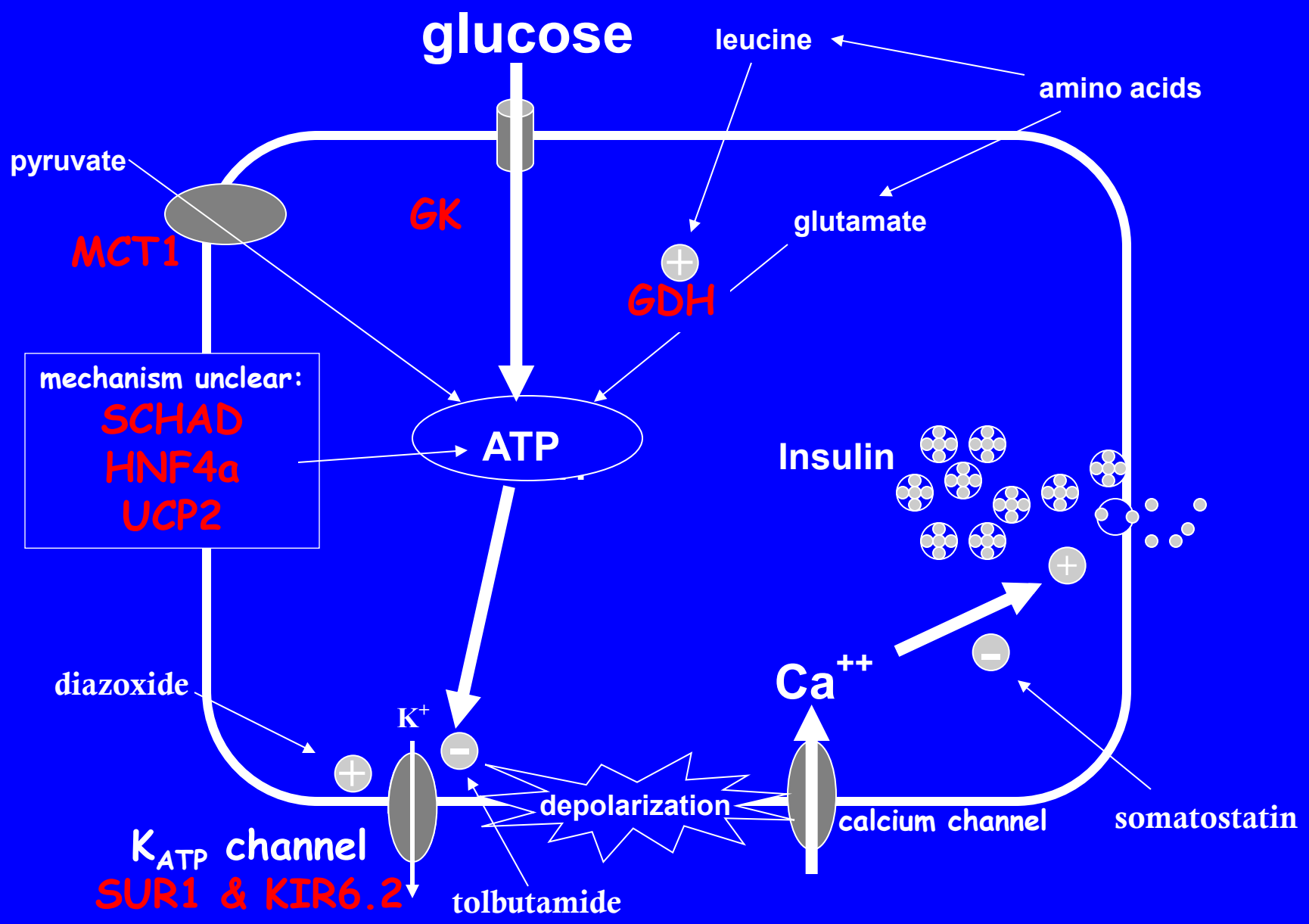
- Protein sensitive hypoglycemia
- Leucine sensitive hypoglycemia
- Nesidioblastosis

Congenital HI is Genetic: Recessive or Dominant Inheritance





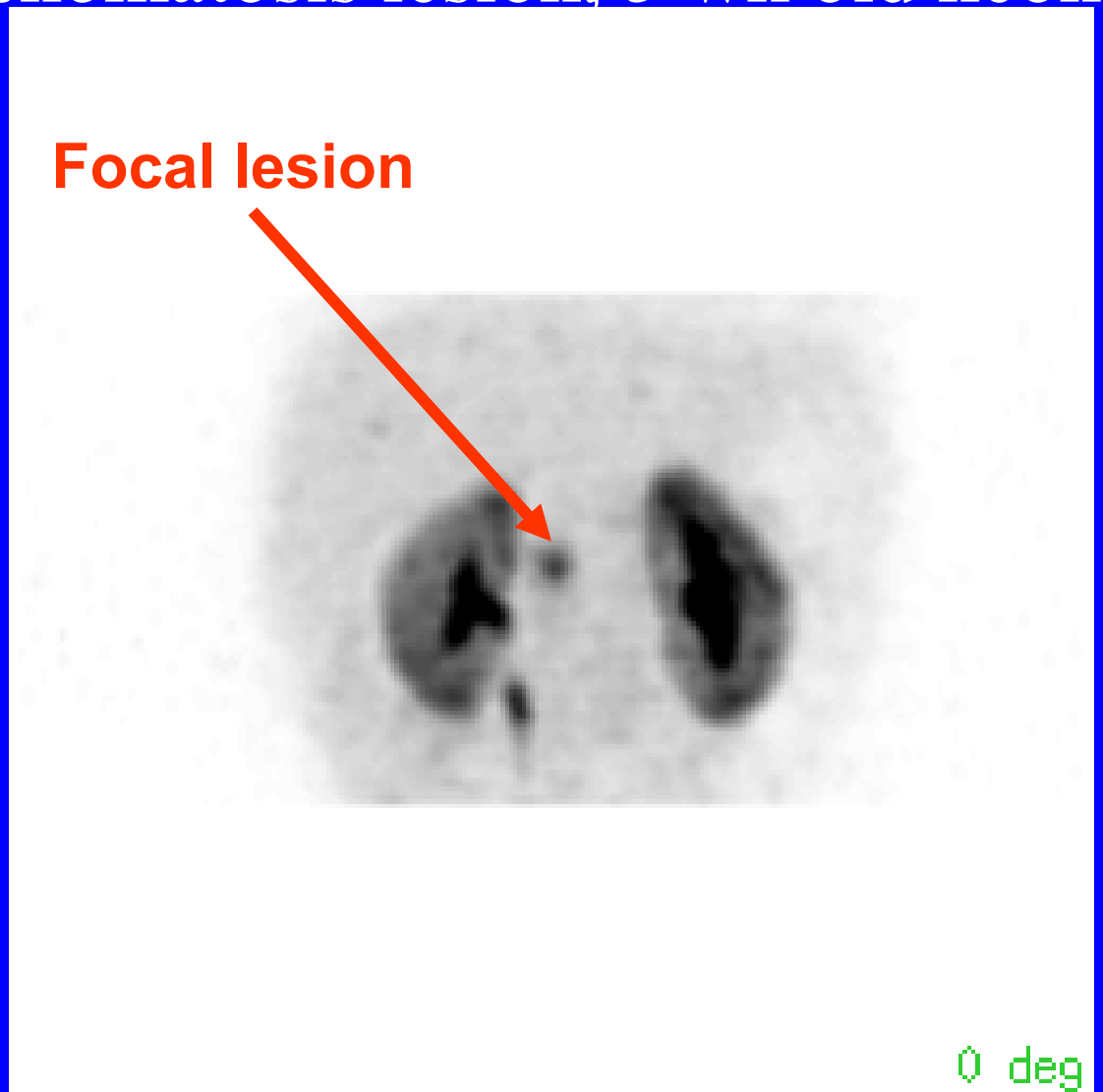
Congenital Hyperinsulinism: Genes



Types of Congenital HI

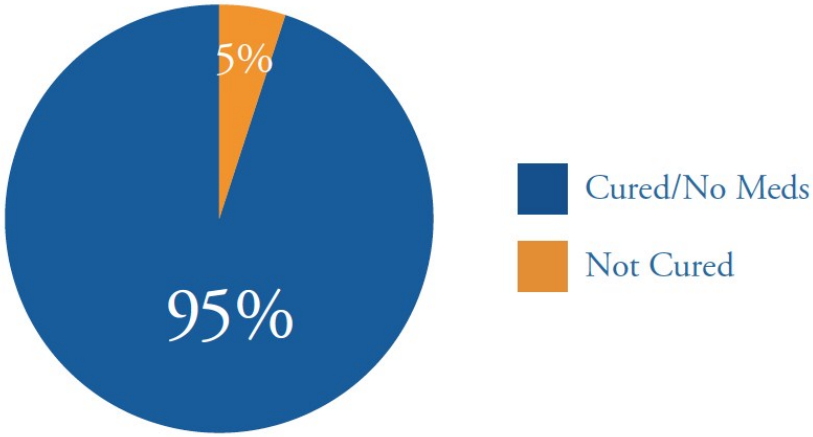
1. Diffuse vs Focal
2. Recessive vs Dominant Inheritance
3. Transient Neonatal (“perinatal stress HI”)

^{18}F-DOPA PET scan localization of focal adenomatosis lesion, 5 wk old neonate

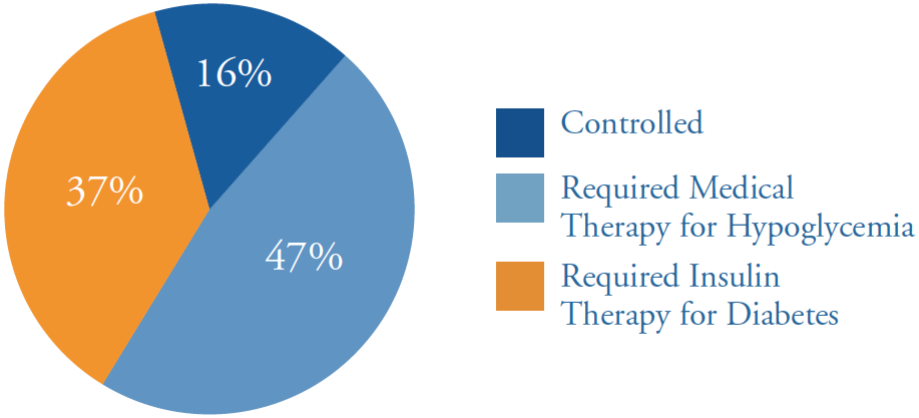


Post-Surgery Outcomes of CHOP Focal vs Diffuse HI

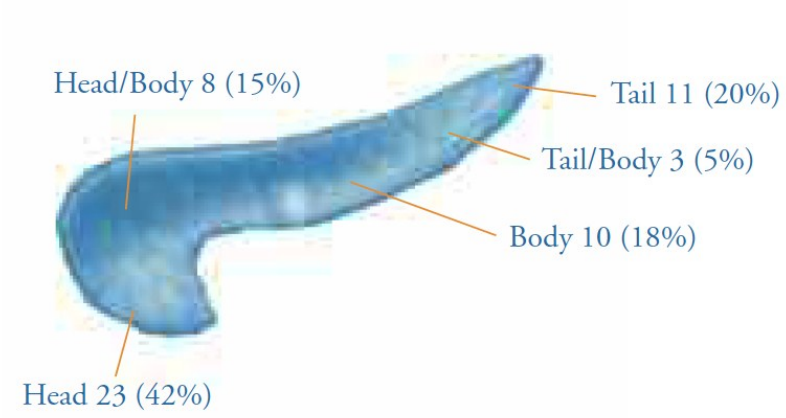
Outcomes of Focal Patients (55 cases)

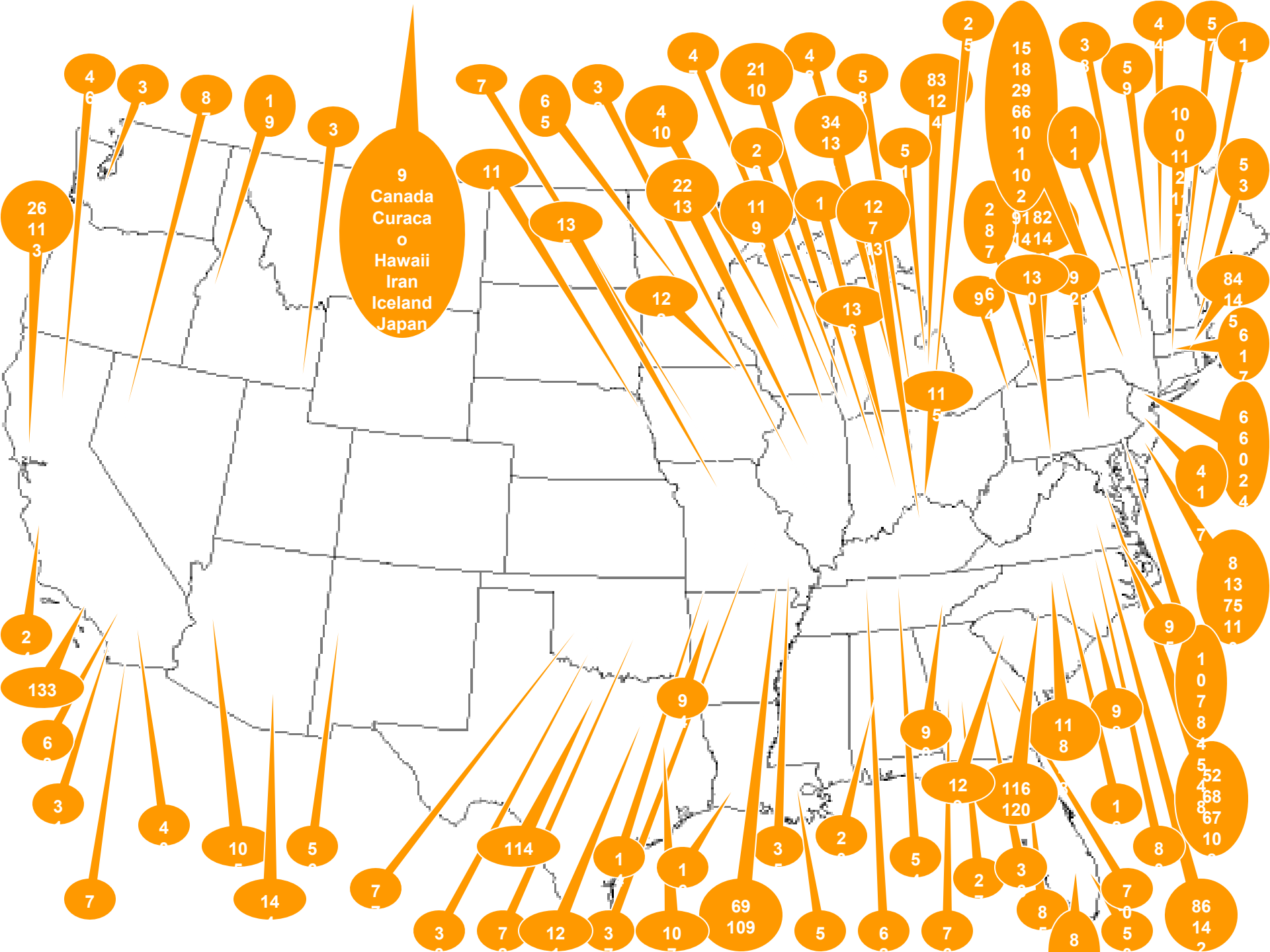


Outcomes of Diffuse Patients (43 cases)



Location of Focal Lesions




9
Canada
Curacao
Hawaii
Iran
Iceland
Japan

Therapies for Hyperinsulinism

1. Surgery
   a) Sub-total pancreatectomy (1950s onward)
   b) Targeted excision of focal lesion (1990s onward)

2. Medical
   a) Diazoxide (1964 onward)
   b) Octreotide (1980s onward)

Diazoxide for Hyperinsulinism

Metabolism

Clinical and Experimental

VOL. XIII, NO. 6 JUNE, 1964

PRELIMINARY REPORT

Drug Therapy in Leucine-Sensitive Hypoglycemia

By ALLAN DRASH AND FREDERICK WOLFF

Reasons for Continued Poor Outcomes in Congenital Hyperinsulinism

1. Delayed Diagnosis
   - Practitioners unaware of entity
   - Lack of physical stigmata*
   - Clinical signs vague/overlooked*
   - Seizures mis-attributed to epilepsy*
   - Confusion about significance of hypoglycemia*
   - Confusion about blood sugar criteria*

2. Inadequate (early) Management*

McQuarrie 1954

Use of lower glucose standards in newborns vs older children/adults

Why?

- –Concern that neonatal hypoglycemia is so common it can't be prevented.
- –Concern about medico-legal liability if standards not kept low.
- –Presumption that asymptomatic hypoglycemia is benign.
- –etc., etc.

Consequence: Hypoglycemia goes unrecognized in the nursery in a third of neonates with severe, uncontrollable hyperinsulinism who require pancreatectomy.

Laboratory testing for hypoglycemia in a seizure?: optional

AAP Section on Neurology, 1997

Practice Parameter: The Neurodiagnostic Evaluation of the Child With a First Simple Febrile Seizure

Blood Studies

Recommendation. **On the basis of published evidence,[7,8,11] the AAP recommends that the following determinations not be performed routinely in the evaluation of a child with a first simple febrile seizure: serum electrolytes, calcium, phosphorus, magnesium, CBC, or blood glucose.**

AMERICAN ACADEMY OF NEUROLOGY

Neurology 2000

PRACTICE PARAMETER: EVALUATING A FIRST NONFEBRILE SEIZURE IN CHILDREN

"Conclusions. The fact that a first nonfebrile seizure occurred in the absence of any suggestive history or symptoms in a child who is older than age 6 months and has returned to baseline has not been shown to be sufficient reason to perform routine laboratory testing in the child with a first nonfebrile seizure."

"Recommendations. • Laboratory tests should be ordered based on individual clinical circumstances that include suggestive historic or clinical findings such as vomiting, diarrhea, dehydration, or failure to return to baseline alertness.12,14,15,20 (Option)"

Idiopathic Hypoglycemia: Report Card 1953-2009

1.	Irreparable brain damage	C-
2.	Delayed diagnosis	C-
3.	Inadequate (early) therapy	C+
4.	Causes	A-
5.	Genetics?	B+

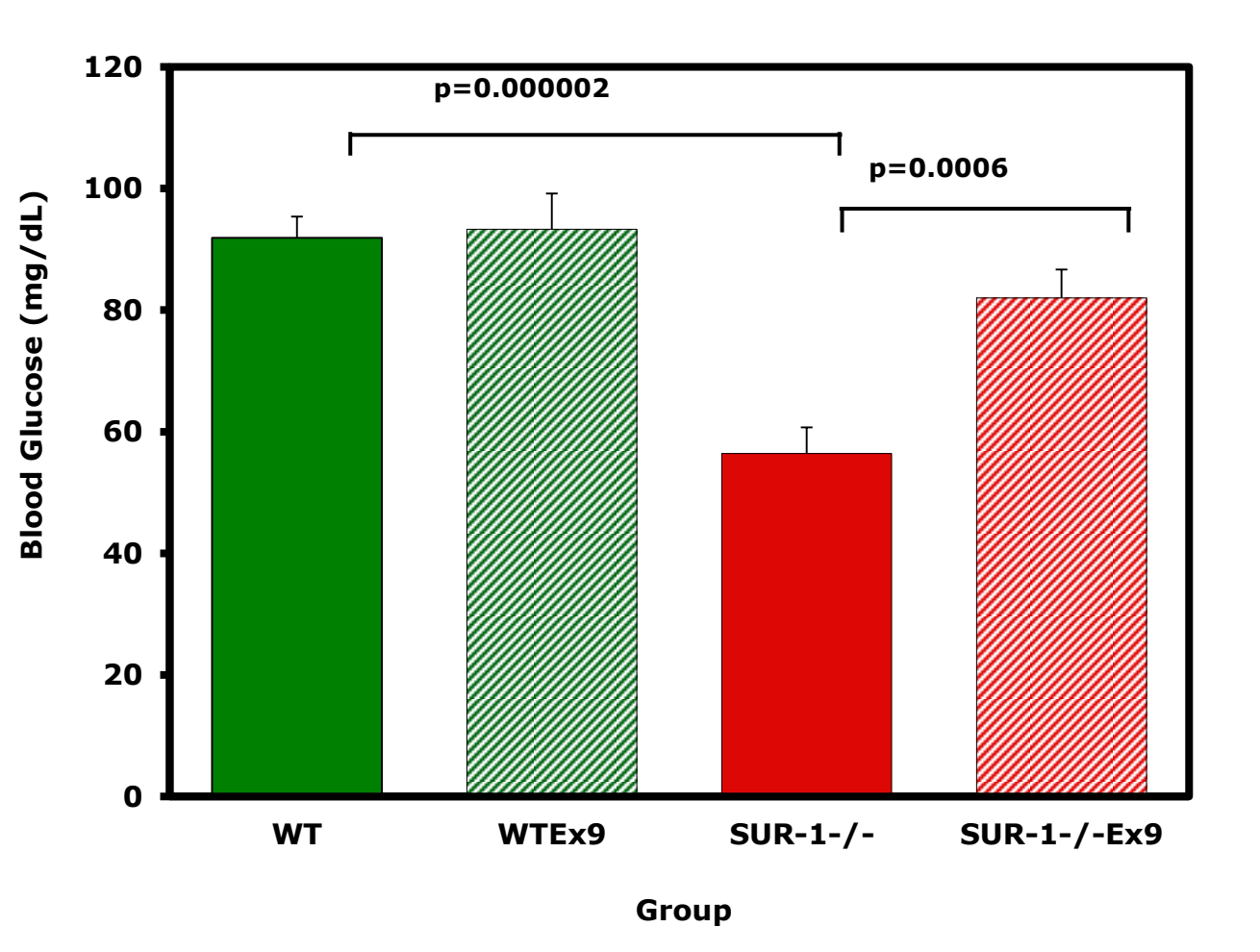
Future of Idiopathic Hypoglycemia (Hyperinsulinism)

1. PET scan localization of focal HI pre-operatively
2. New drugs needed (e.g. Exendin-(9-39))
3. More HI genes to find: McQuarrie's cases
4. Etiology of peri-natal stress HI to discover
5. Earlier recognition and treatment still needed

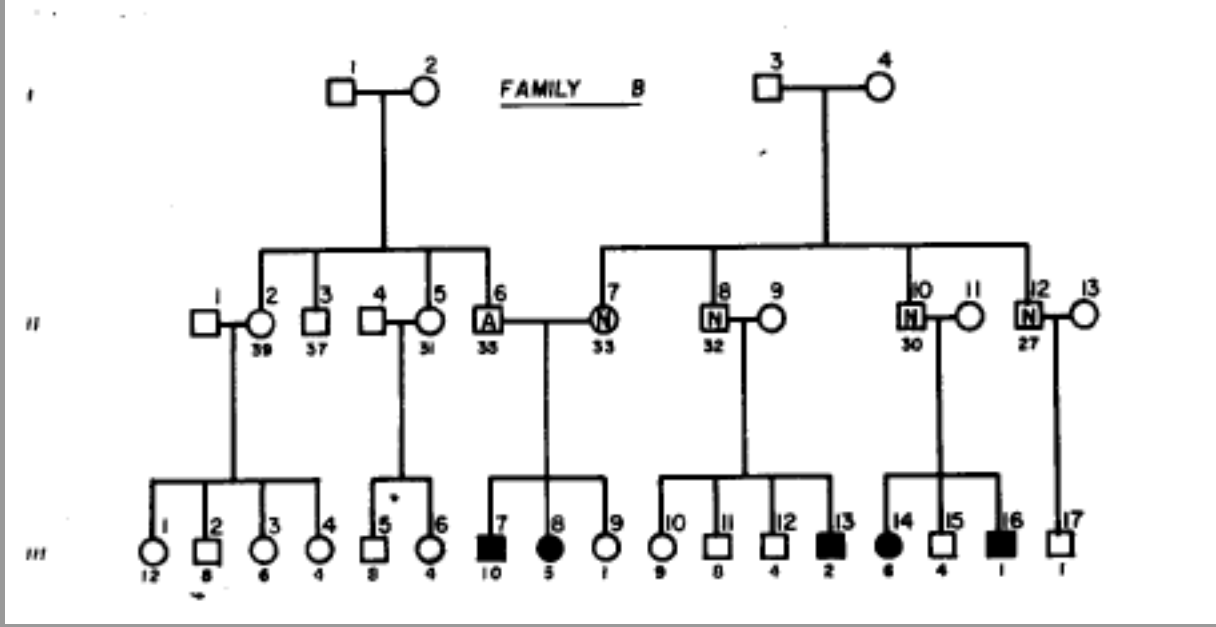
Lizard Spit for HI?

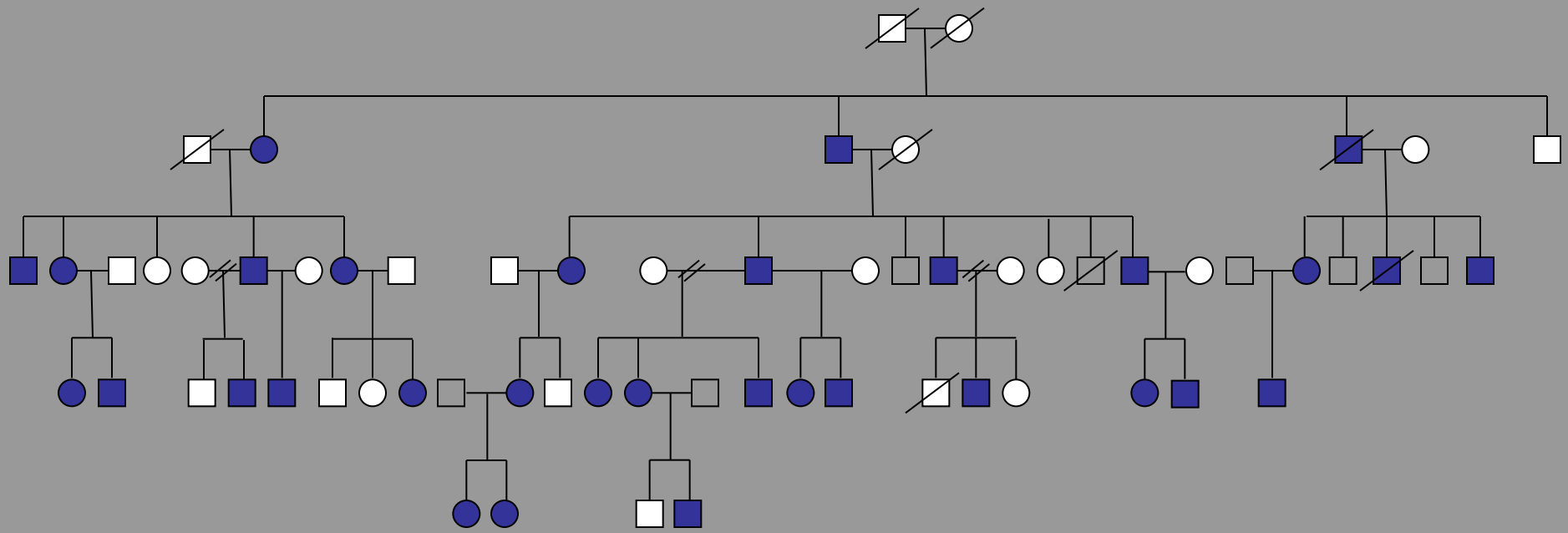
Exendin-(9-39) = GLP-1 antagonist

Exendin-(9-39) corrects fasting hypoglycemia in *SUR1*$^{-/-}$ mice

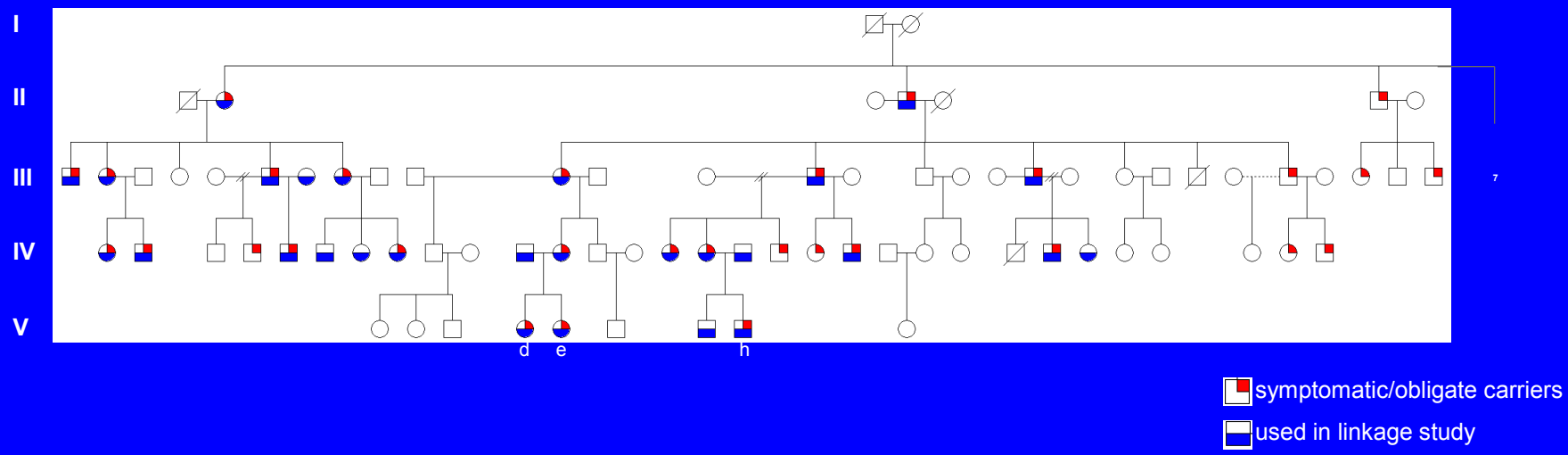


De León, et al. J Biol Chem, 2008





Sara Pinney 2008


I
II
III
IV
V
d
e
h
symptomatic/obligate carriers
used in linkage study


49 genes
63,950,212
(cent)
72,318,547
(tel)
ZNF365
EGR2
NRBF2
JMJD1C
REEP3
CTNNA3
DNAJC12
SIRT1
LRRTM3
HERC4
MYPN
ATOH7
PBLD
HNRPH3
RUFY2
DNA2L
CXXC6
CCAR1
SLC25A16
STOX1
DDX50
DDX21
SRGN
VPS26A
SUPV3L1
KIAA1279
HKDC1
HK1
TACR2
TSPAN15
NEUROG3
C10orf35
COL13A1
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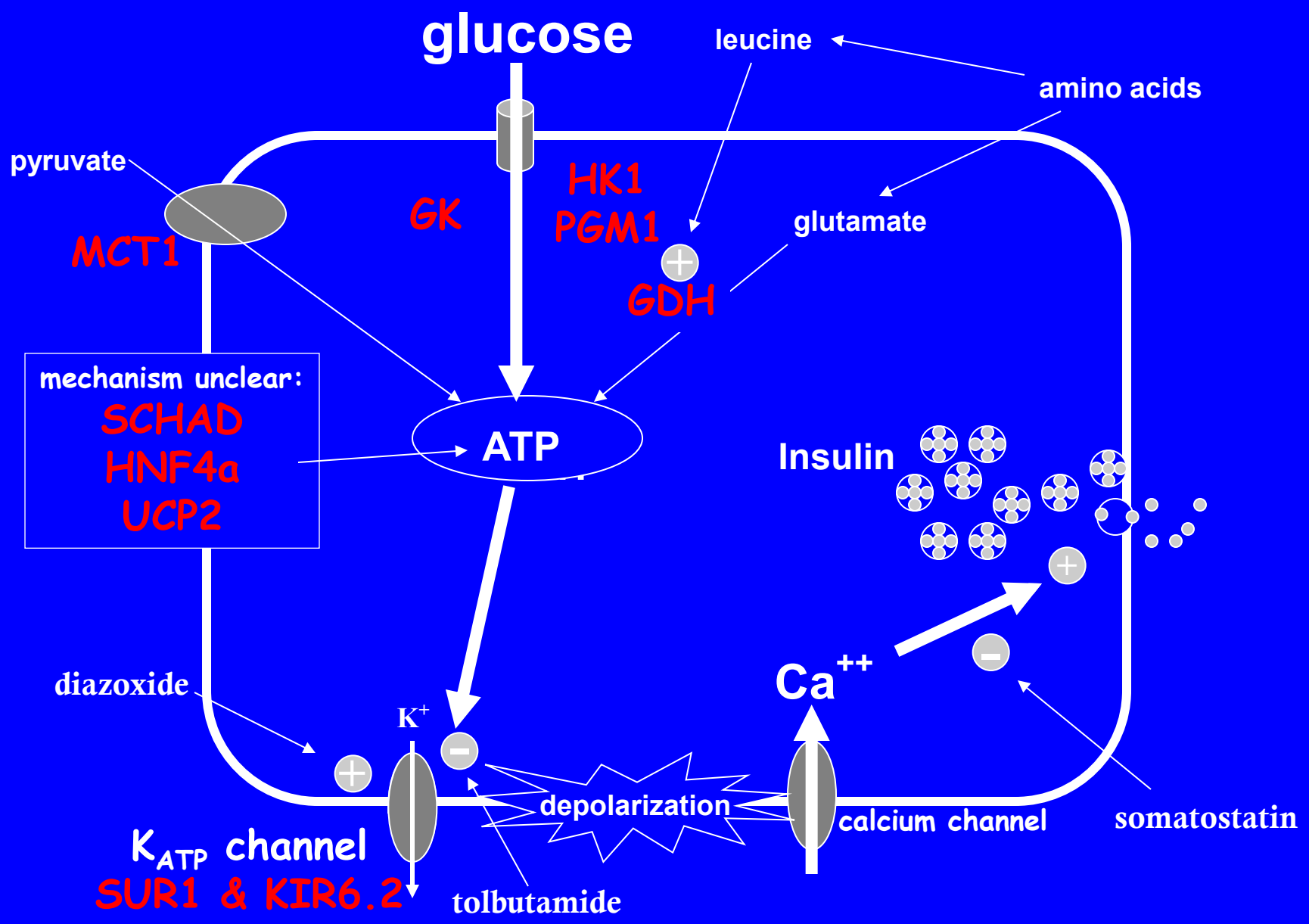
PCBD1

Congenital Hyperinsulinism: Genes



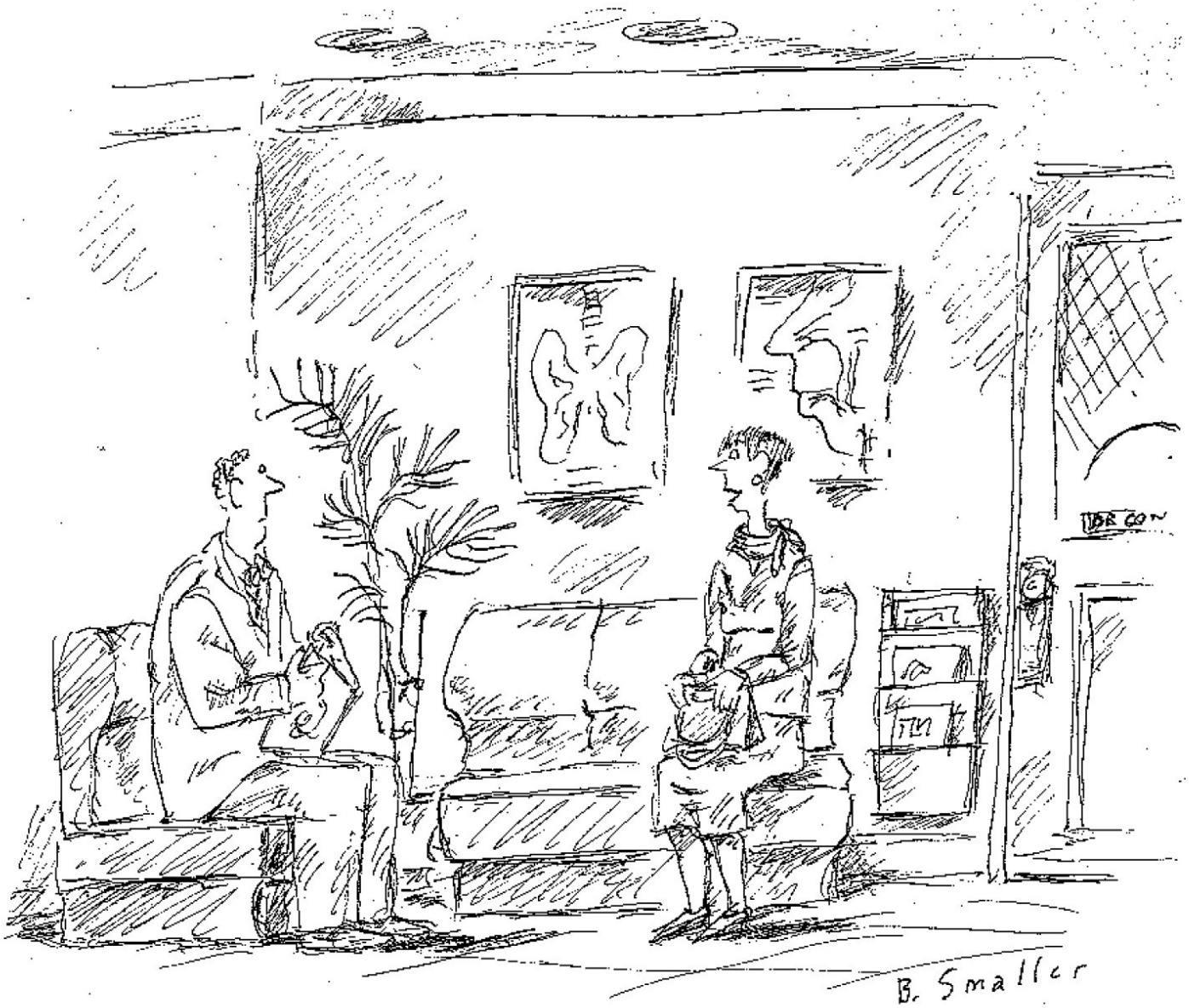
CHI and the Future of HI

1. Advocacy (improved detection & early treatment, barriers to treatment, research funds)

2. Networking (family support, education, other rare disease groups, etc)

3. Fund-raising (research, training, patient assistance, public awareness)

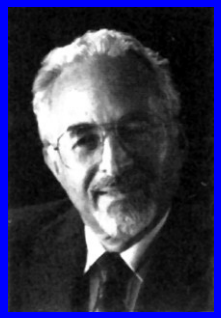
4. etc., etc., etc……



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

end

Acknowledgements



Lester Baker

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