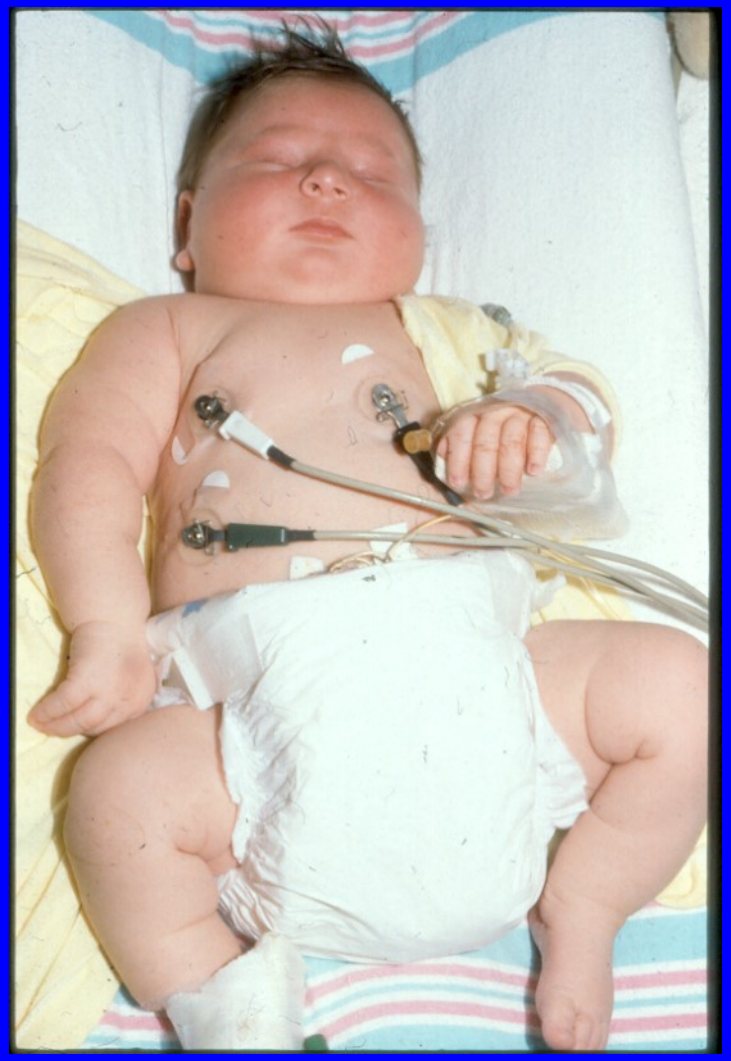
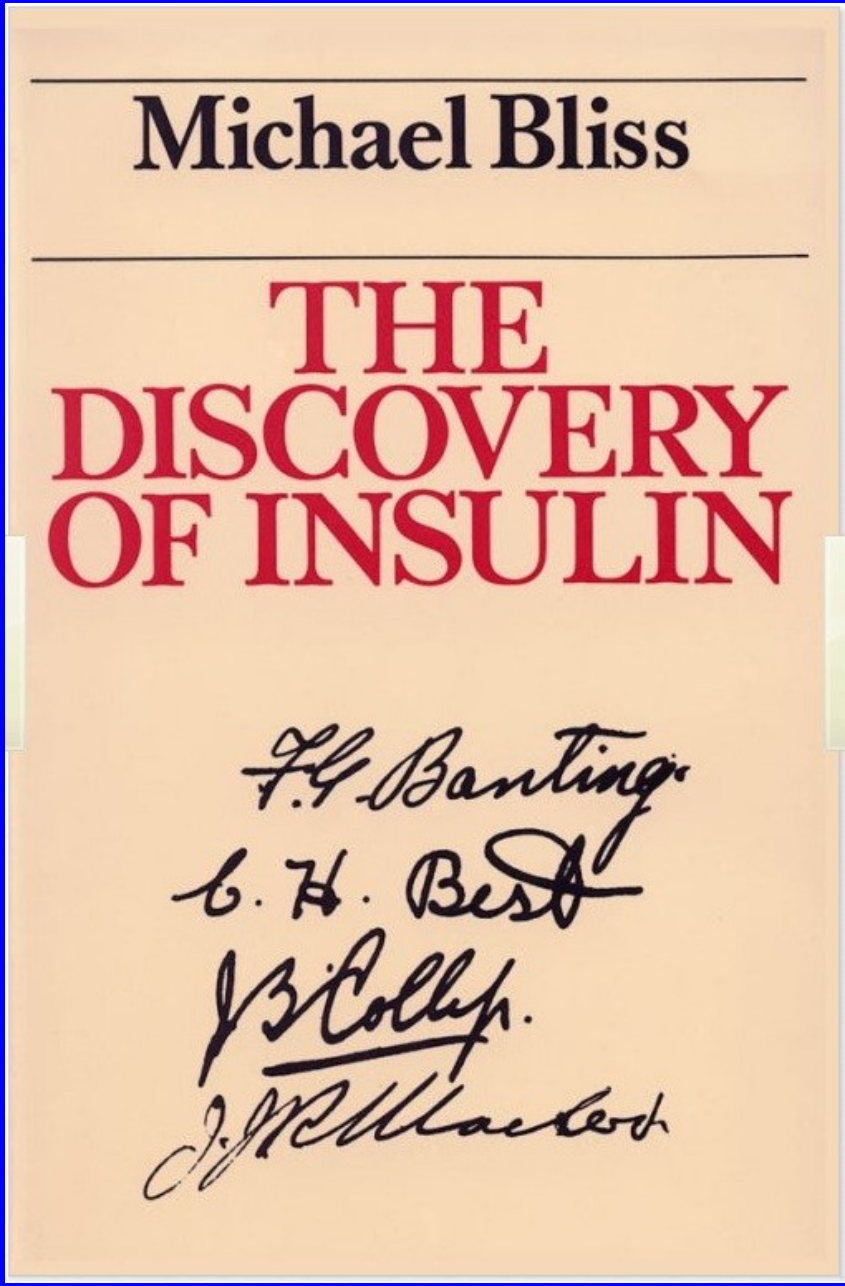
History of Hyperinsulinism (HI) in Pediatrics and Overview of Diagnostic/Therapeutic Algorithm



Charles A. Stanley, MD
CHOP HI Center

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



In the Beginning……1954

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.

"…My seemingly impulsive decision to (choose this title) was the direct result of my seeing the seventh young child….who had suffered irreparable brain damage from severe hypoglycemia….four were examples of severe spontaneous hypoglycemia in infants who were victims of delayed diagnosis and inadequate early therapy…."

McQuarrie 1954

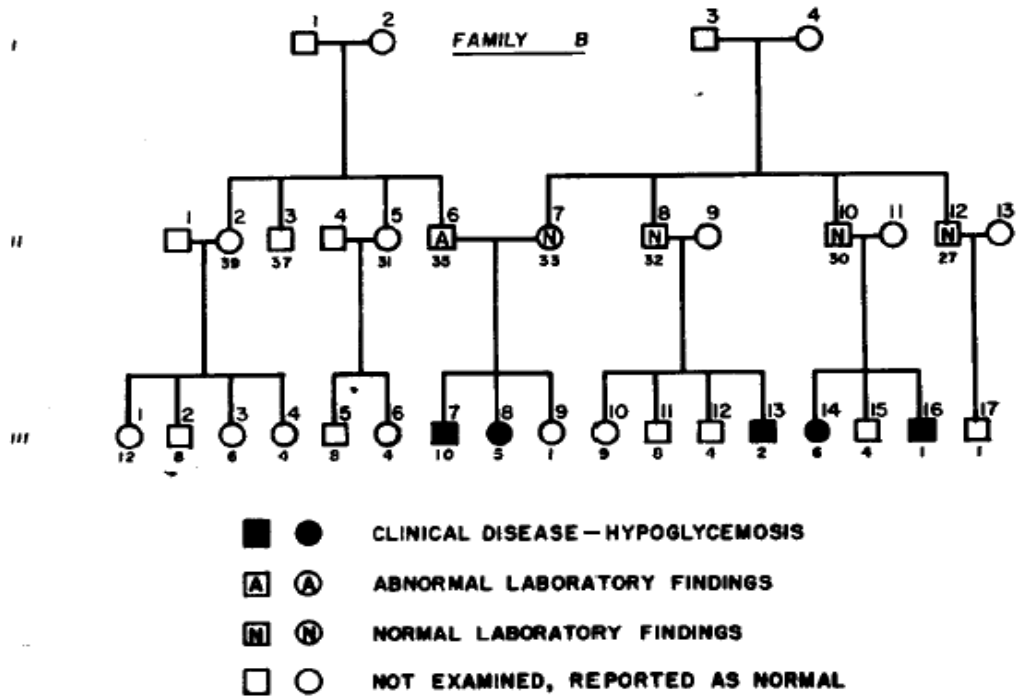


Fig. 2.—Genetic factor in the syndrome of idiopathic spontaneous hypoglycemia. Family A, pedigree of the R. family. Family B, pedigree of the W. family (J. G., B. G., J. W., and P. W.).

Familial

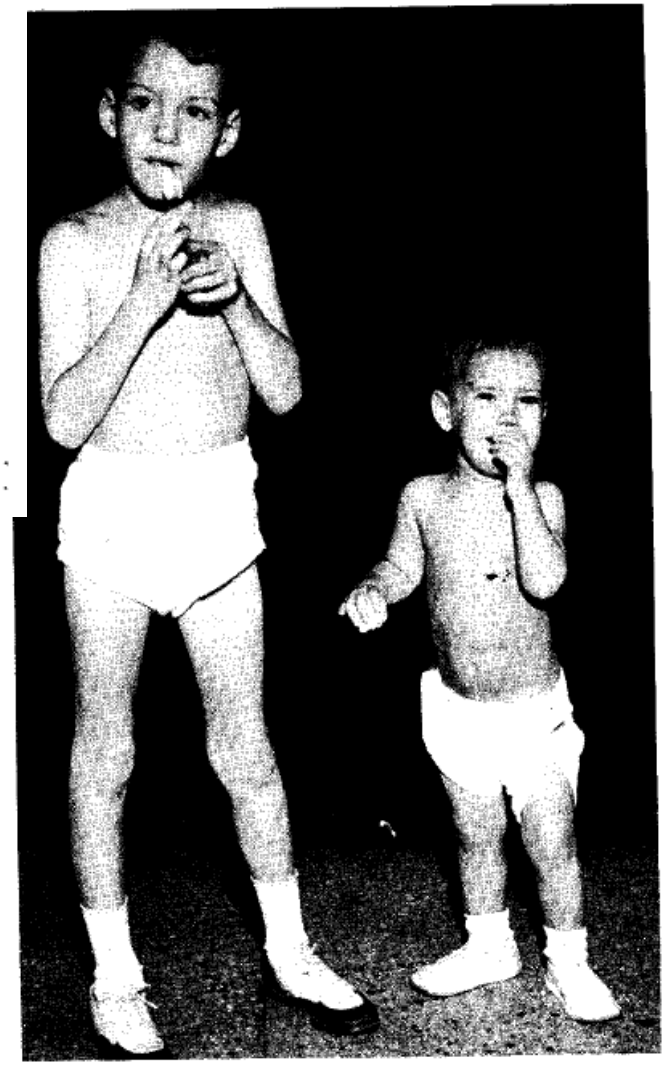
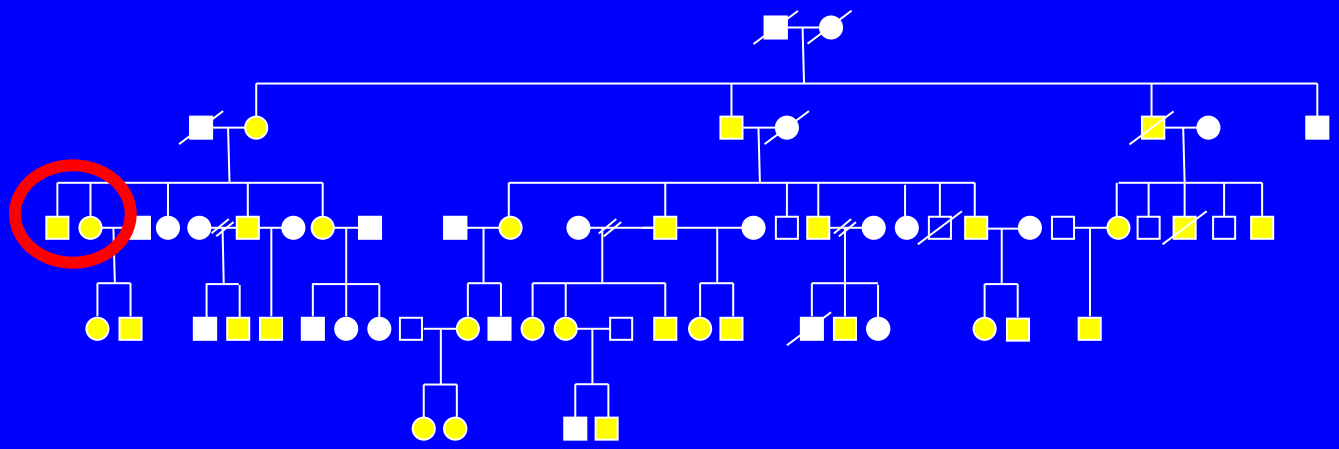
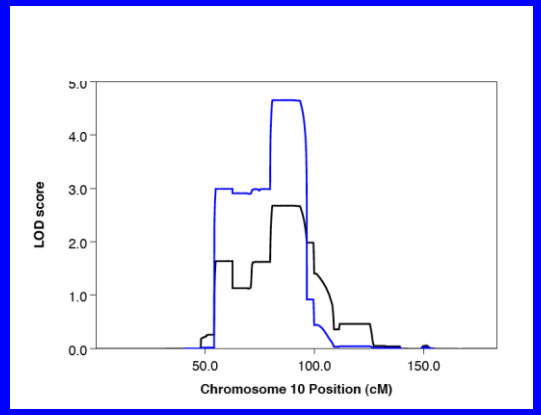


Fig. 3.—Photograph of J. G., aged 6 years, and B. G., aged 15 months. Ta
after beginning of corticotropin therapy. Pancreatic resection scars visible.

Hexokinase 1 Mutations in McQuarrie's Hyperinsulinism W Family

Dominant Form of Congenital Hyperinsulinism Maps to HK1 Region on 10q. S E Pinney, K Ganapathy, J Bradfield, D Stokes, A Sasson, K Mackiewicz, K Boodhansingh, N Hughes, S Becker, S Givler, C Macmullen, D Monos, A Ganguly, H Hakonarson, CA Stanley. Horm Res Paediatr 2013





49 genes – 8.3 Mb region

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, H2AFY2, AIFM2, TYSND1, SARA1, PPA1, NPFFR1, LRRC20, EIF4EBP2, NODAL, KIAA1274, PRF1, ADAMTS14, C10orf27, SGPL1, PCBD1

Idiopathic Hypoglycemia of Infancy:
McQuarrie's Findings

1. Possibly genetic?

2. Irreparable brain damage
   a) Delayed diagnosis
   b) Inadequate therapy

1. Limited treatment options (pancreatectomy / glucocorticoids)

1955

Hypoglycemia induced by protein feeding, especially leucine (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)

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

1960

Discovery of Hyperinsulinemia in Leucine Sensitive Idiopathic Hypoglycemia of Infancy

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

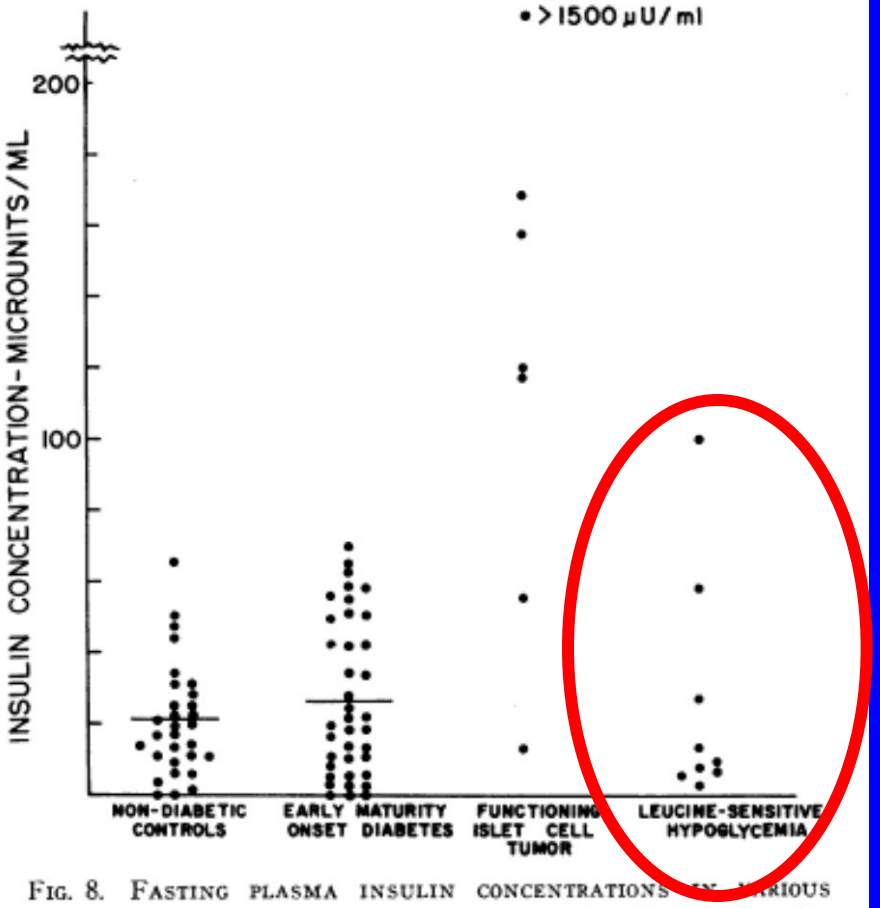


FIG. 8. FASTING PLASMA INSULIN CONCENTRATIONS IN VARIOUS GROUPS OF SUBJECTS. The subject with plasma insulin concentration greater than 1,500 μU per ml had an islet cell adenocarcinoma with widespread metastases (patient of Dr. J. Field).

N.B.: not always clearly elevated!

1964

Diazoxide for Treatment of Hyperinsulinism (Drash & Wolff 1964)

Metabolism

Clinical and Experimental

VOL. XIII, NO. 6 JUNE, 1964

PRELIMINARY REPORT

Drug Therapy in Leucine-Sensitive Hypoglycemia

By ALLAN DRASH AND FREDERICK WOLFF

1975

"Idiopathic Hypoglycemia" becomes "Congenital Hyperinsulinism" (Haymond & Pagliara; Stanley & Baker; Aynsley-Greene)

Criteria for Clinical Diagnosis Hyperinsulinism:

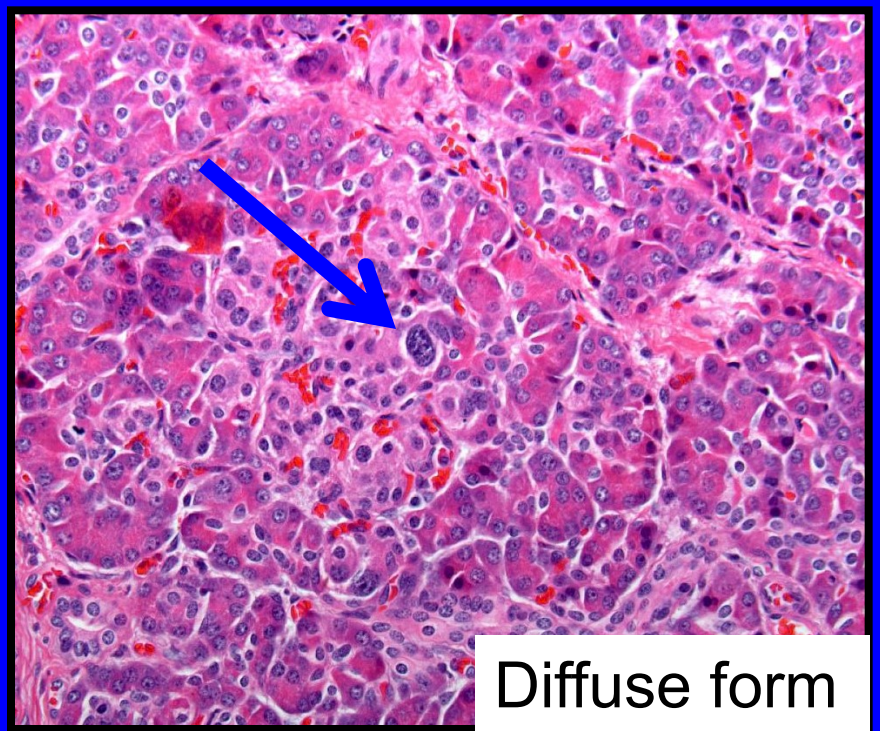
1. Hyper-Insulinemia
2. Hypo-Ketonemia
3. Hypo-FFA-emia
4. Hyper-Glycemic response to Glucagon

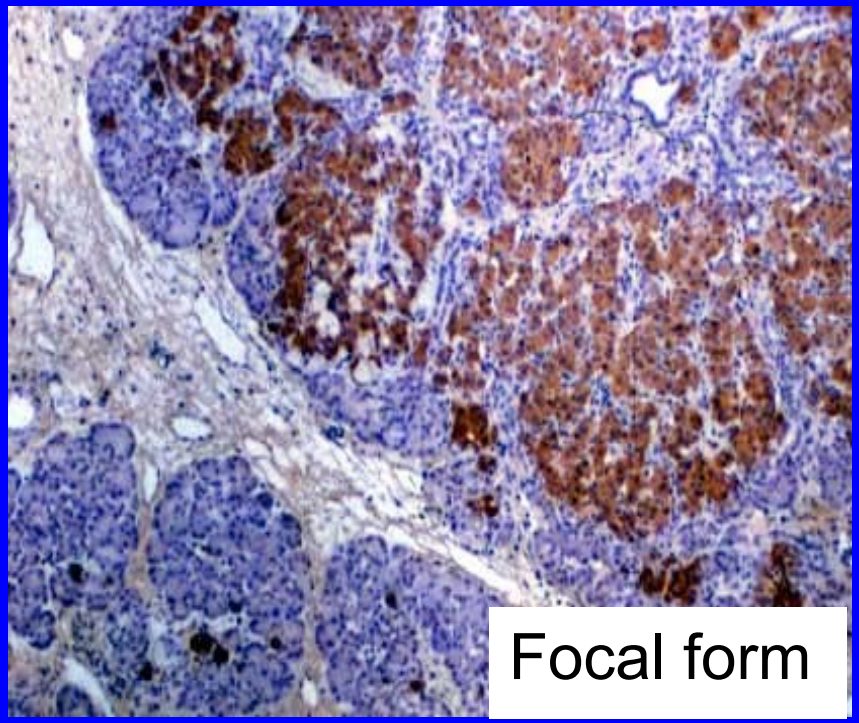
1981

Realization that Hyperinsulinism is not a Disorder of Embryogenesis ("Nesidioblastosis")

(Jaffe R, Hashida Y, Yunis EJ. Lab Invest. 1980
Rahier, Wallon, Henquin. Diabetologia 1981)

Recognition of Two Types of Hyperinsulinism: Diffuse and Focal (Brunelle, Fekete, Saudubray, et al 1989)





1990 - 2000

Development of Centers of Excellence for HI

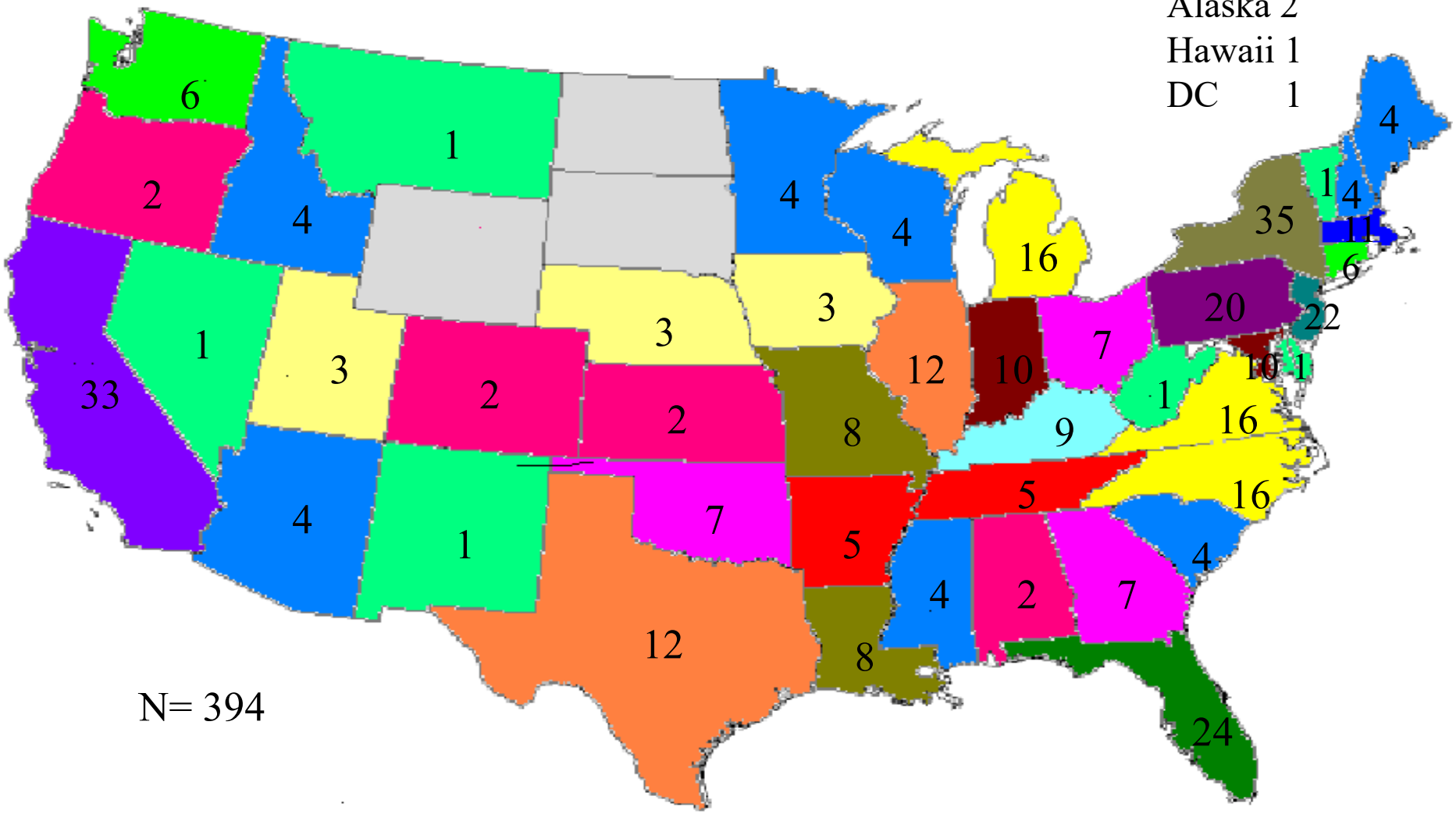
- France
- England (2)
- Israel
- USA (2)
- Germany
- Australia, China, etc…….

CHOP Hyperinsulinism Center Team

http://hyperinsulinism.chop.edu

215-590-7682 hyperinsulin@email.chop.edu

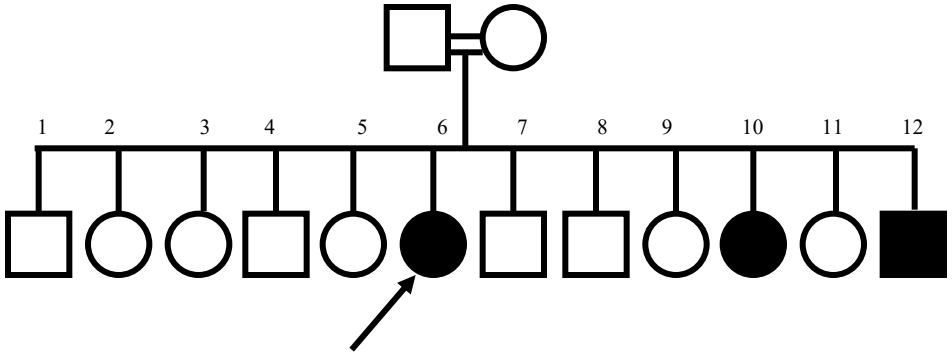
Surgical HI Patient Origins

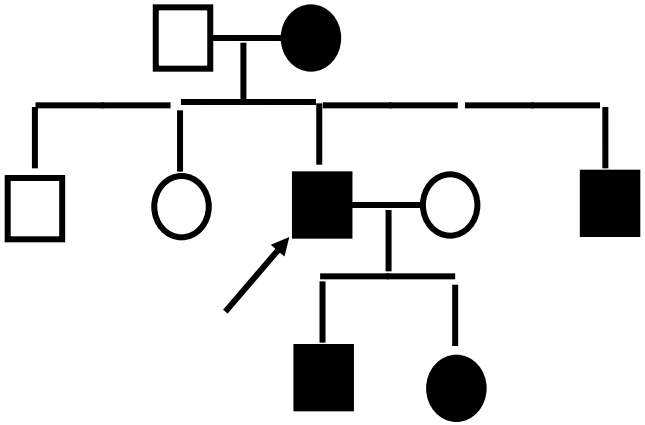


Argentina 1 Australia 1 Brazil 1 Canada 13 Colombia 1 Curacao 1 Ecuador 2
Iran 1 Israel 2 Japan 1 Panama 1 Paraguay 1 Saudi Arabia 1 Singapore 1 Venezuela 1

1995

Congenital HI is Genetic: Recessive or Dominant Inheritance

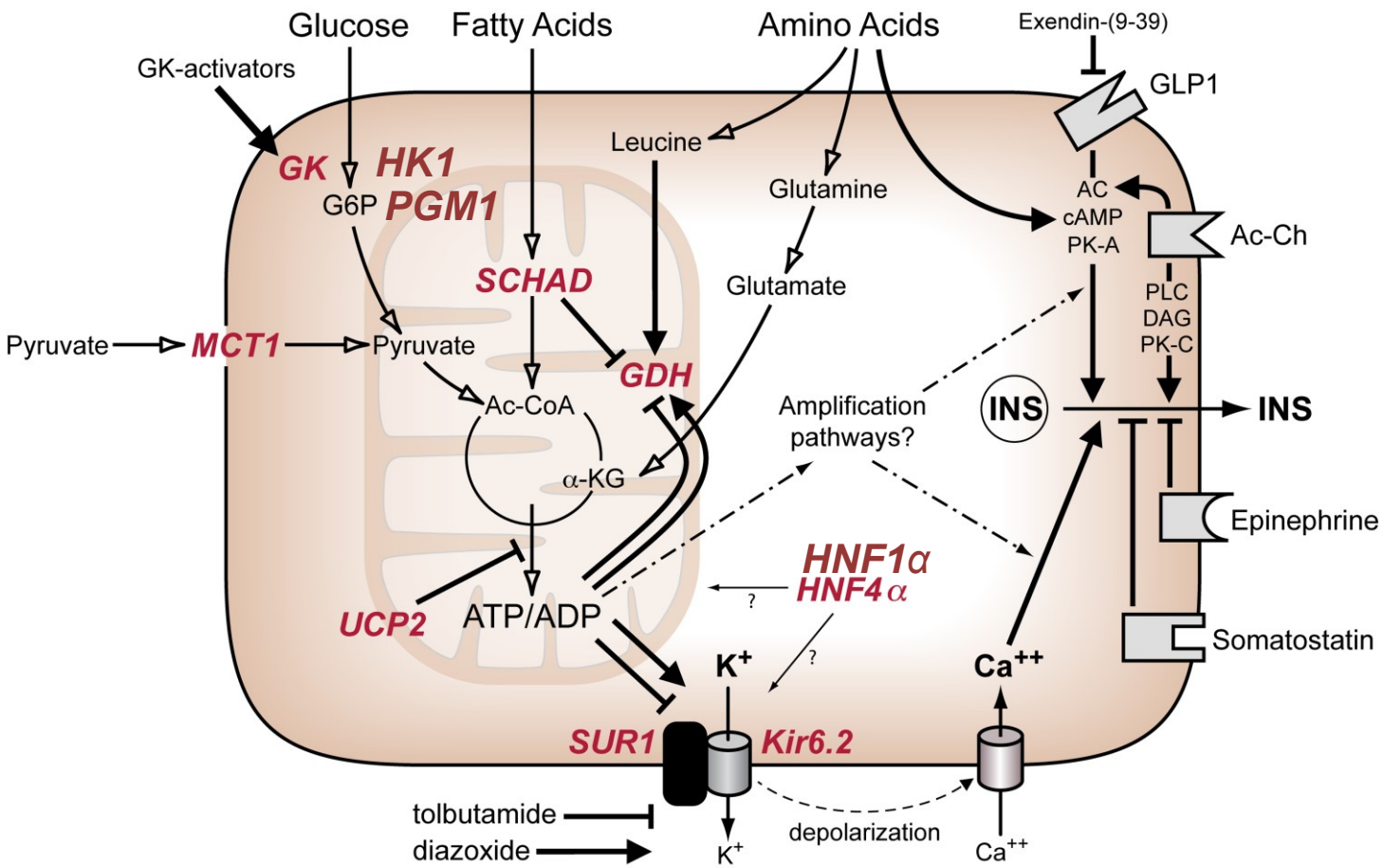




1995

The Genetic Era of Hyperinsulinism begins with Discovery of Sulfonylurea Receptor Channel Mutations

(Bryan, Aguilar-Bryan, Thomas, Gagel, Glaser, Permutt, Stanley, Thornton, etc.)



Phenotypes of Congenital Hyperinsulinism

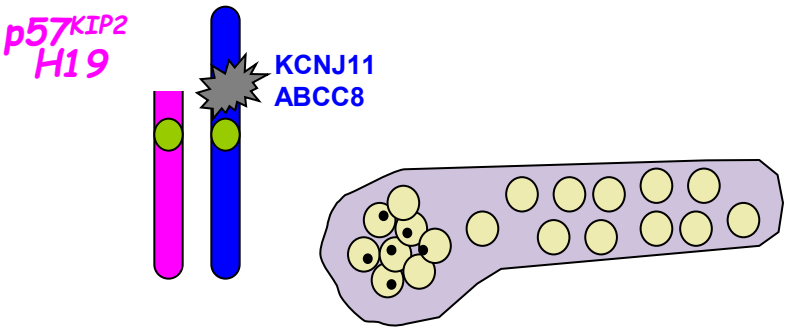
gene	genetics	Sensitivity to stimuli / inhibitors				
		diazoxide	protein	leucine	calcium	exercise
KATP	rec	-	+	-	+	-
KATP	dom	+	+	-	+	-
GDH (HI-HA)	dom	+	+	+	-	-
GCK	dom	-	-	-	-	-
SCHAD	rec	+	+	+	-	+
MCT1	dom	?	-	-	-	+
HNF4a	dom	+	?	?	?	-
UCP2	dom	+	-	-	-	-
Peri-natal stress	NA	+	-	-	-	-

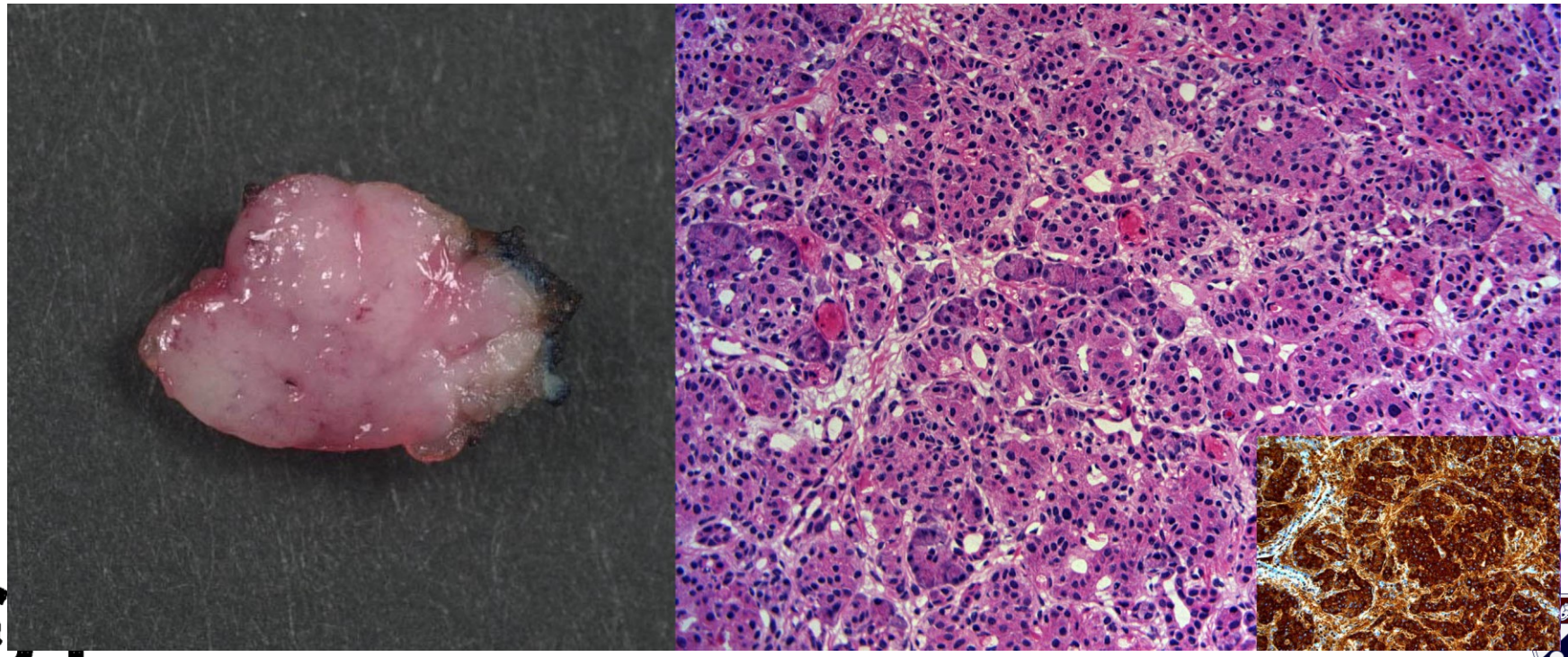
Focal HI

Genetic cause - two hit mechanism:

1) Paternal mutation found in all tissues
2) LOH of maternal allele on 11p including KATP genes and growth regulatory genes

Result: Uncontrolled islet cell proliferation forming a focal lesion which constitutively secretes insulin due to a knock out paternal mutation





Parental Genotyping

Predicting Focal-HI

	Focal-HI	Diffuse-HI
Single recessive KATP mutation	144	9
No single recessive KATP mutation	4	95

A single heterozygous recessive mutation accurately predicts focal-HI:

Sensitivity: 97%
Specificity: 91%

When paternal inheritance is confirmed:

Sensitivity: 97%
Specificity: 93%

2006

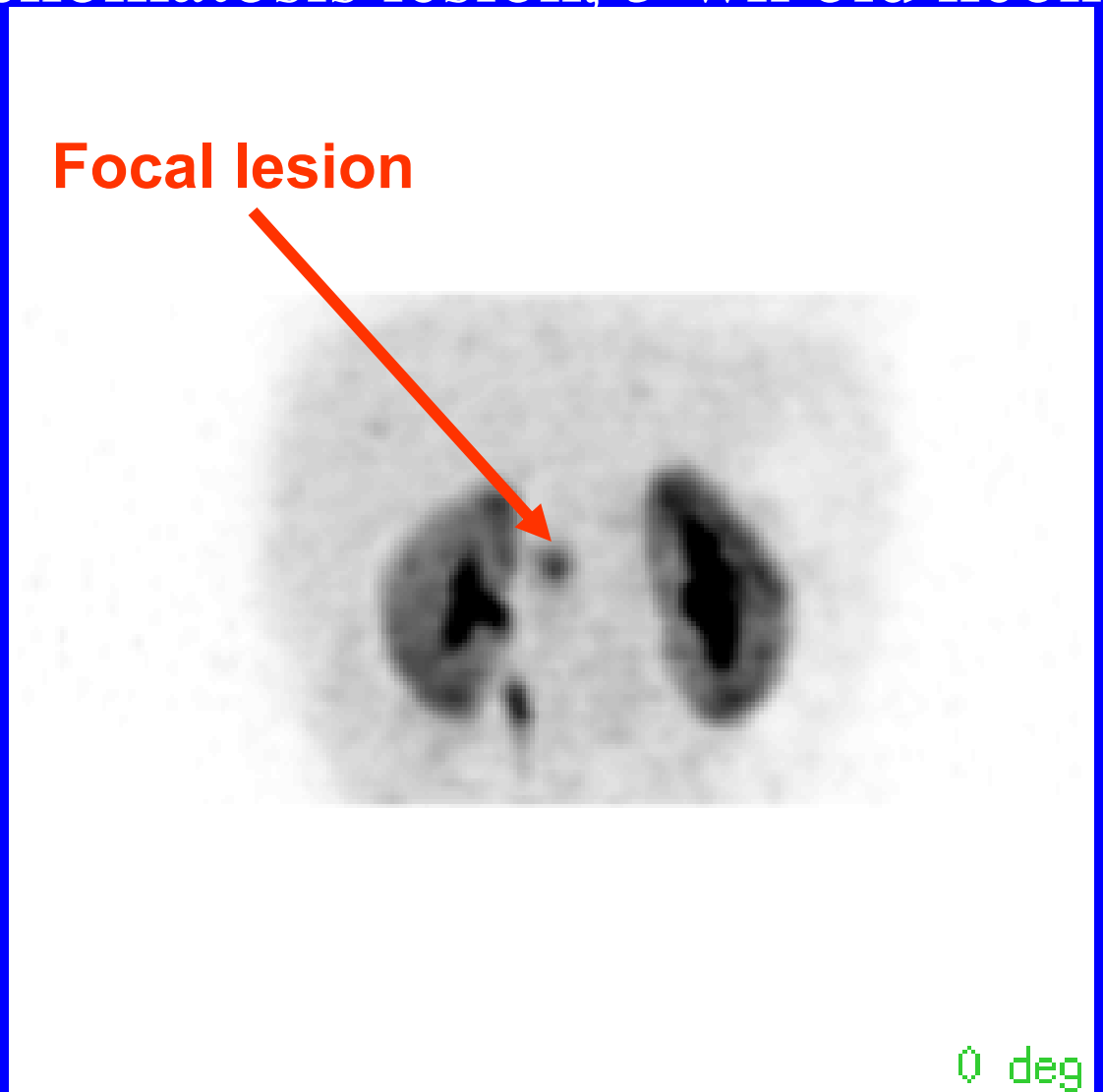
^{18}Fluoro-DOPA PET Imaging for focal HI

Original Article

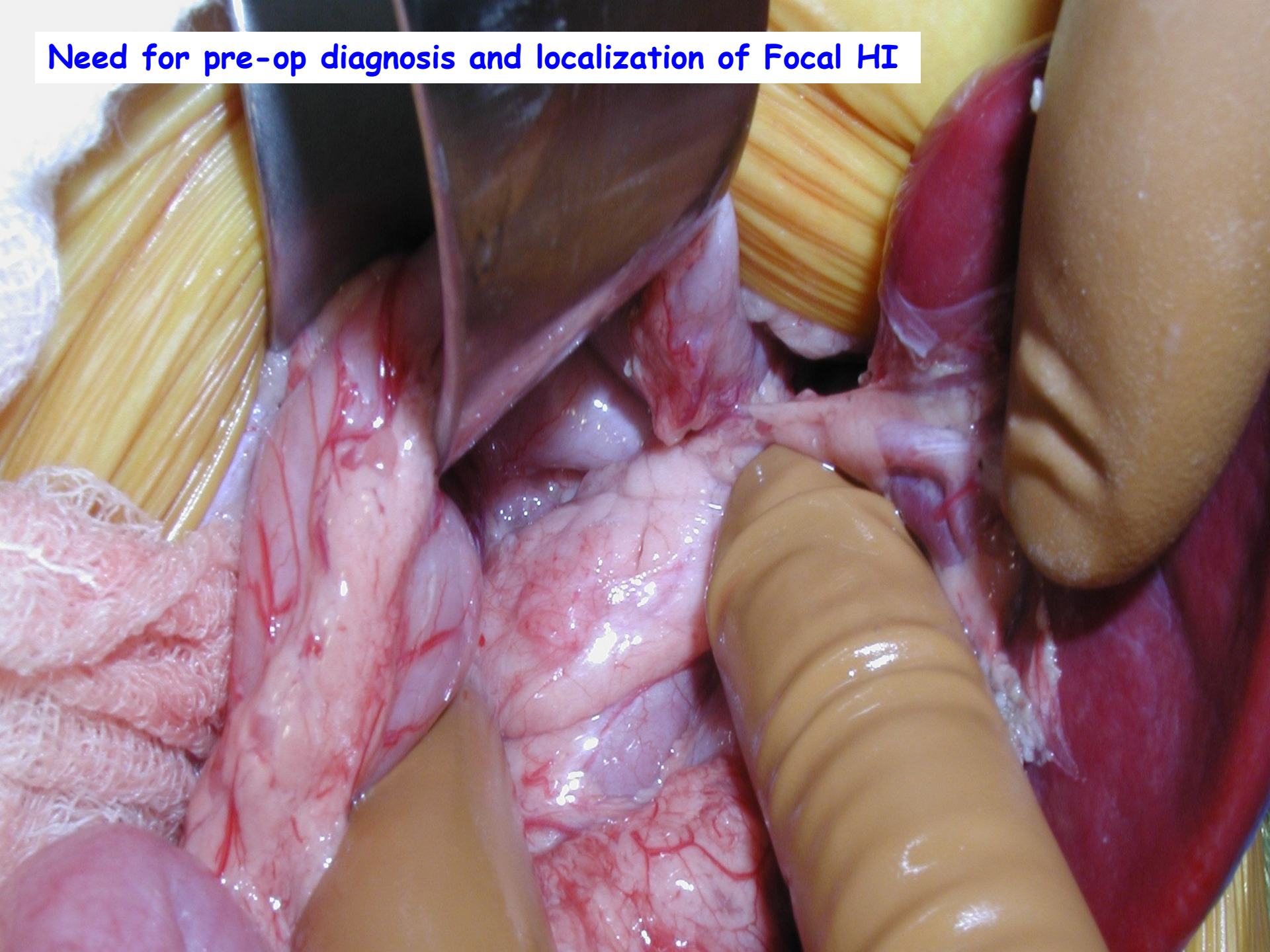
Noninvasive Diagnosis of Focal Hyperinsulinism of Infancy With [^{18}F]-DOPA Positron Emission Tomography

Timo Otonkoski,[1] Kirsti Näntö-Salonen,[2] Marko Seppänen,[3] Riitta Veijola,[4] Hanna Huopio,[5] Khalid Hussain,[6] Päivi Tapanainen,[4] Olli Eskola,[3] Riitta Parkkola,[2] Klas Ekström,[7] Yves Guiot,[8] Jacques Rahier,[8] Markku Laakso,[5] Risto Rintala,[1] Pirjo Nuutila,[3] and Heikki Minn[3]

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

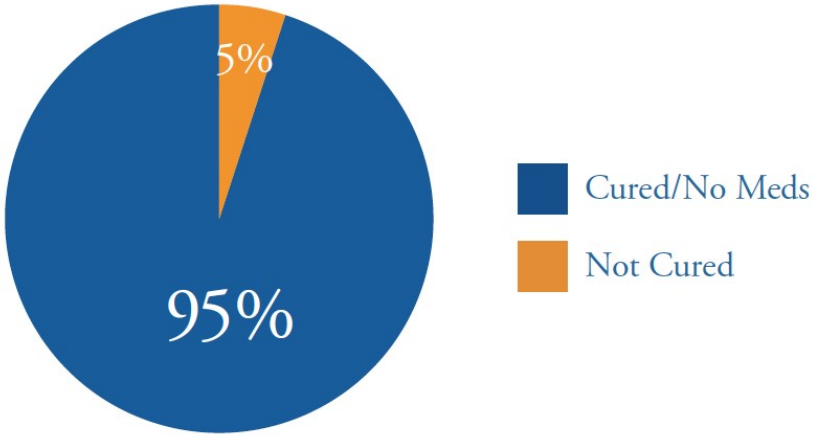


Need for pre-op diagnosis and localization of Focal HI

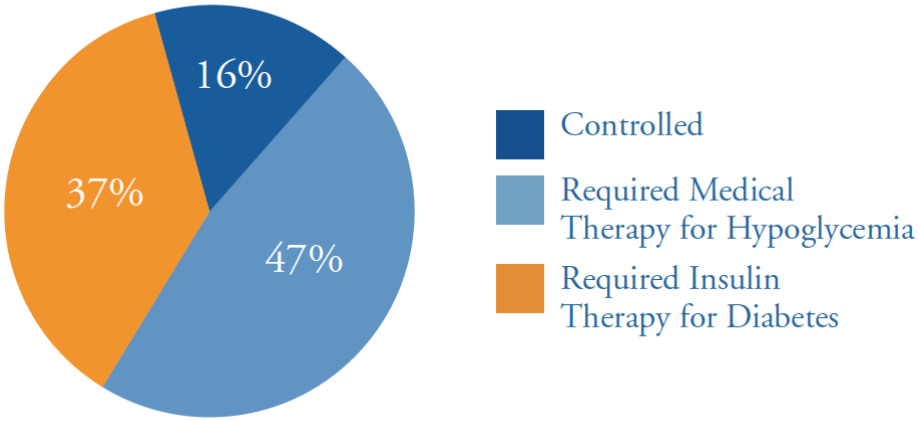


Post-Surgery Outcomes of CHOP Focal vs Diffuse HI

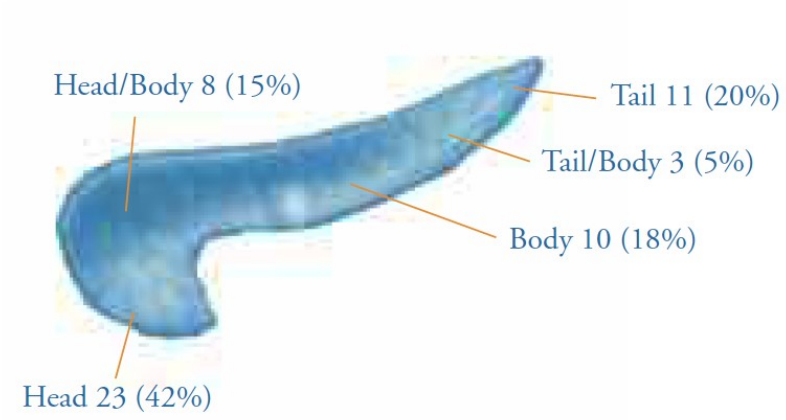
Outcomes of Focal Patients (55 cases)



Outcomes of Diffuse Patients (43 cases)



Location of Focal Lesions



2015

New Guidelines for Hypoglycemia Disorders in Neonates, Infants, and Children from the PES (free on-line!!)

MEDICAL PROGRESS www.jpeds.com • THE JOURNAL OF PEDIATRICS

Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children

Paul S. Thornton, MB, BCh[1], Charles A. Stanley, MD[2], Diva D. De Leon, MD, MSCE[2], Deborah Harris, PhD[3], Morey W. Haymond, MD[4], Khalid Hussain, MD, MPH[5], Lynne L. Levitsky, MD[6], Mohammad H. Murad, MD, MPH[7], Paul J. Rozance, MD[8], Rebecca A. Simmons, MD[9], Mark A. Sperling, MBBS[10], David A. Weinstein, MD, MMSc[11], Neil H. White, MD[12], and Joseph I. Wolfsdorf, MB, BCh[13]

COMMENTARY www.jpeds.com • THE JOURNAL OF PEDIATRICS

Re-Evaluating "Transitional Neonatal Hypoglycemia": Mechanism and Implications for Management

Charles A. Stanley, MD[1], Paul J. Rozance, MD[2], Paul S. Thornton, MB, BCh[3], Diva D. De Leon, MD[1], Deborah Harris, PhD[4], Morey W. Haymond, MD[5], Khalid Hussain, MD, MSc[6], Lynne L. Levitsky, MD[7], Mohammad H. Murad, MD, MPH[8], Rebecca A. Simmons, MD[9], Mark A. Sperling, MBBS[10], David A. Weinstein, MD[11], Neil H. White, MD[12], and Joseph I. Wolfsdorf, MB, BCh[13]

http://www.ncbi.nlm.nih.gov/pubmed/25819173

http://www.ncbi.nlm.nih.gov/pubmed/25957977

HI Treatment Options 1985-now

Medical:

- Diazoxide
- Octreotide
- Continuous tube feedings

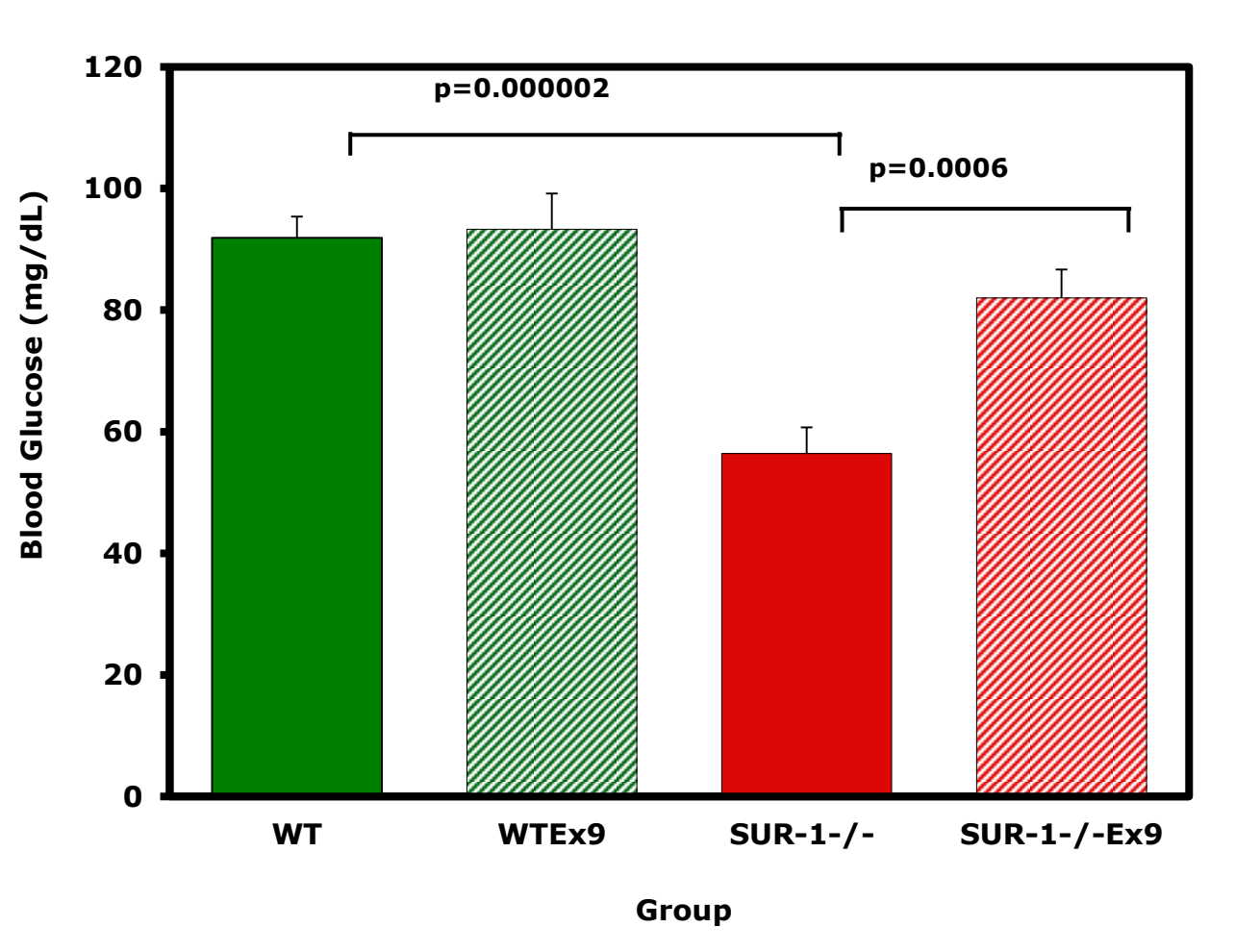
Surgery

- Diffuse: near-total pancreatectomy
- Focal: cure by excision

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

Futuristic HI Treatments

- Long-acting Octreotide (Paris, Germany)
- GLP-1 receptor antagonist (Philly)
- Sirolimus (London)
- ….at least 3 other potential agents in the pre-clinical pipeline (…that I know about!:
  - IR antibody (XOMA)
  - Soluble Glucagon for pumps (XERIS)

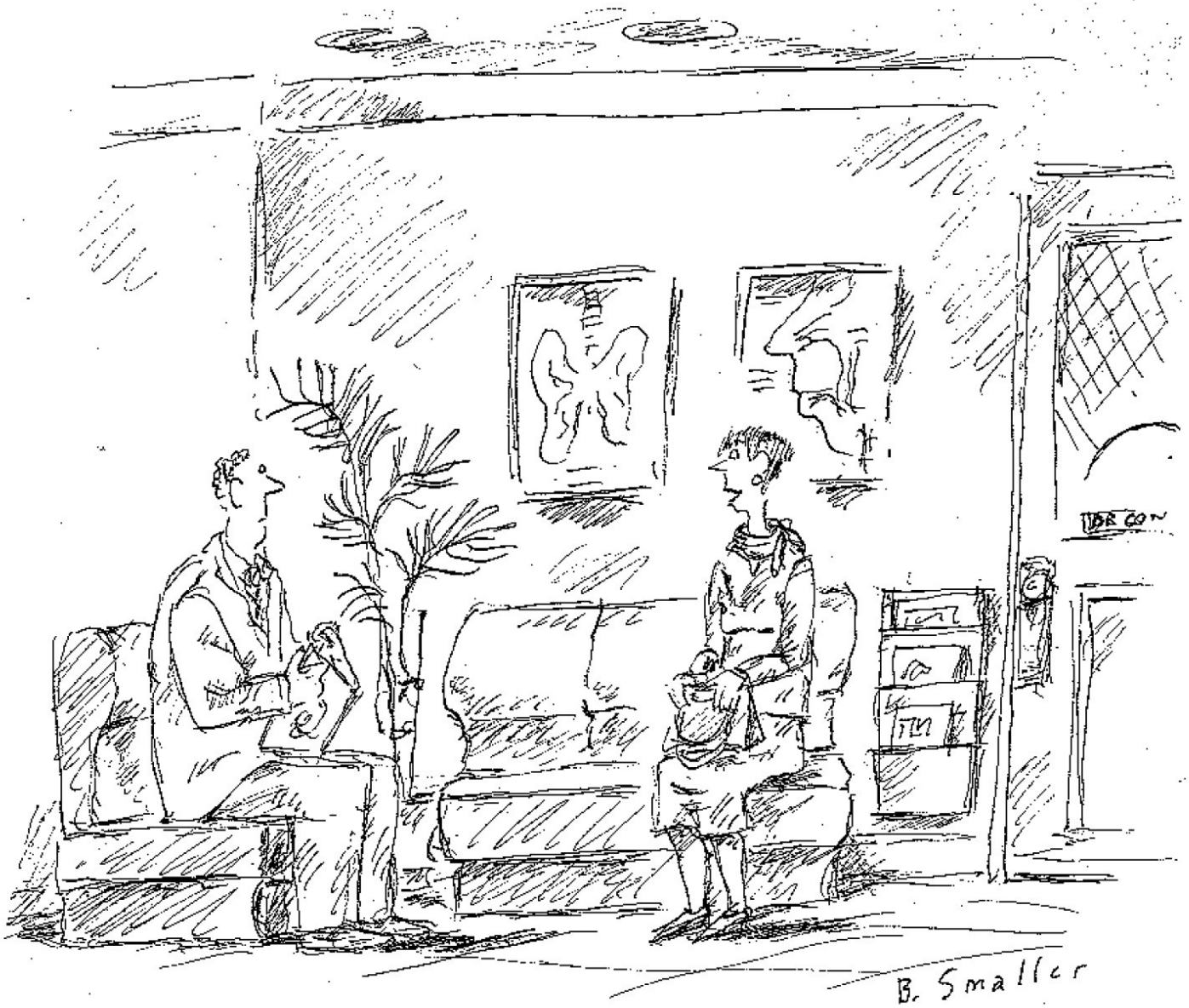
CHI and the Future of HI

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

2. Networking (family support, education, other rare disease groups, HI patient registry…)

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

4. etc., etc., etc……

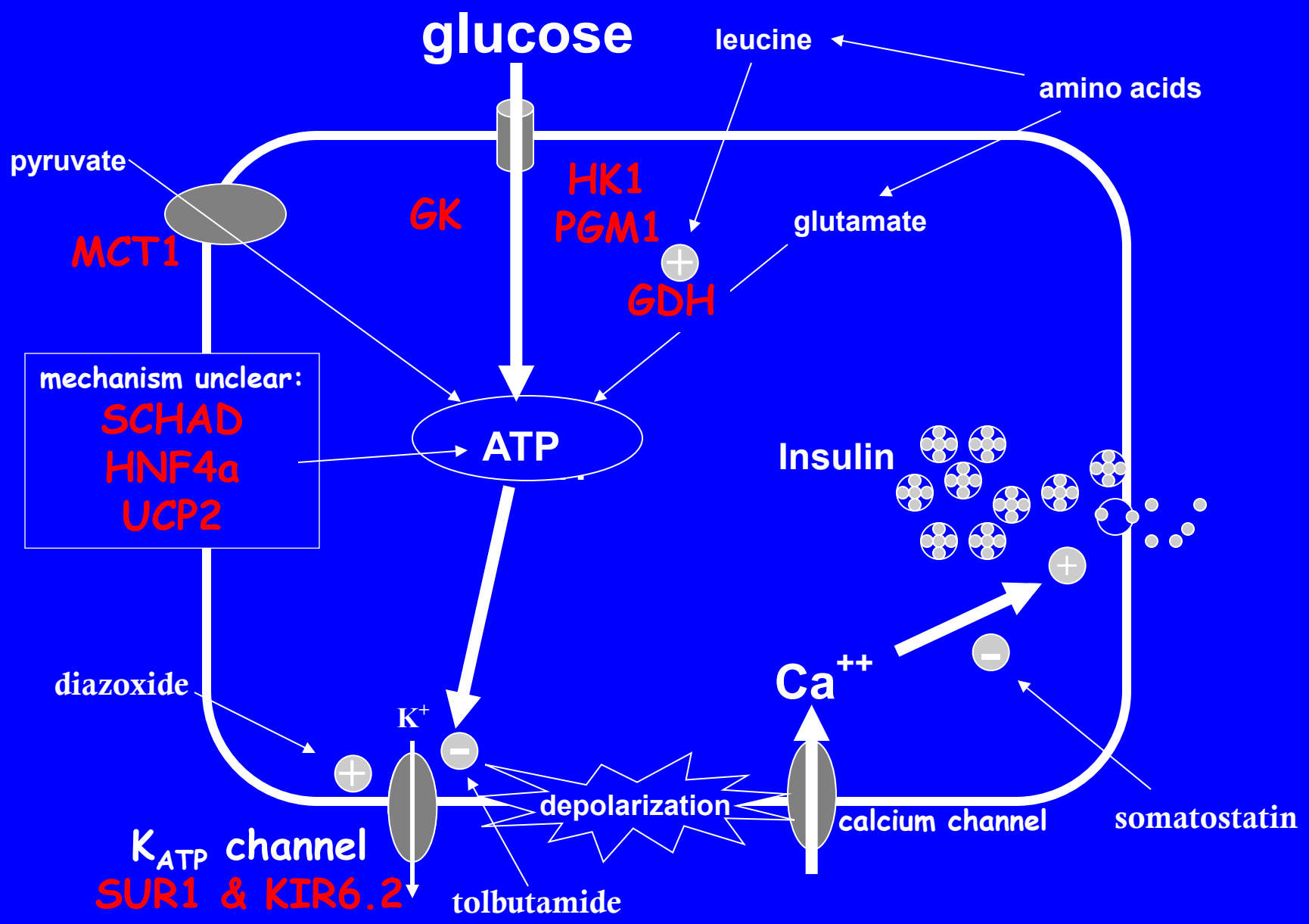


"It's a very rare disease—it doesn't have a cure. It doesn't even have a spokesperson."

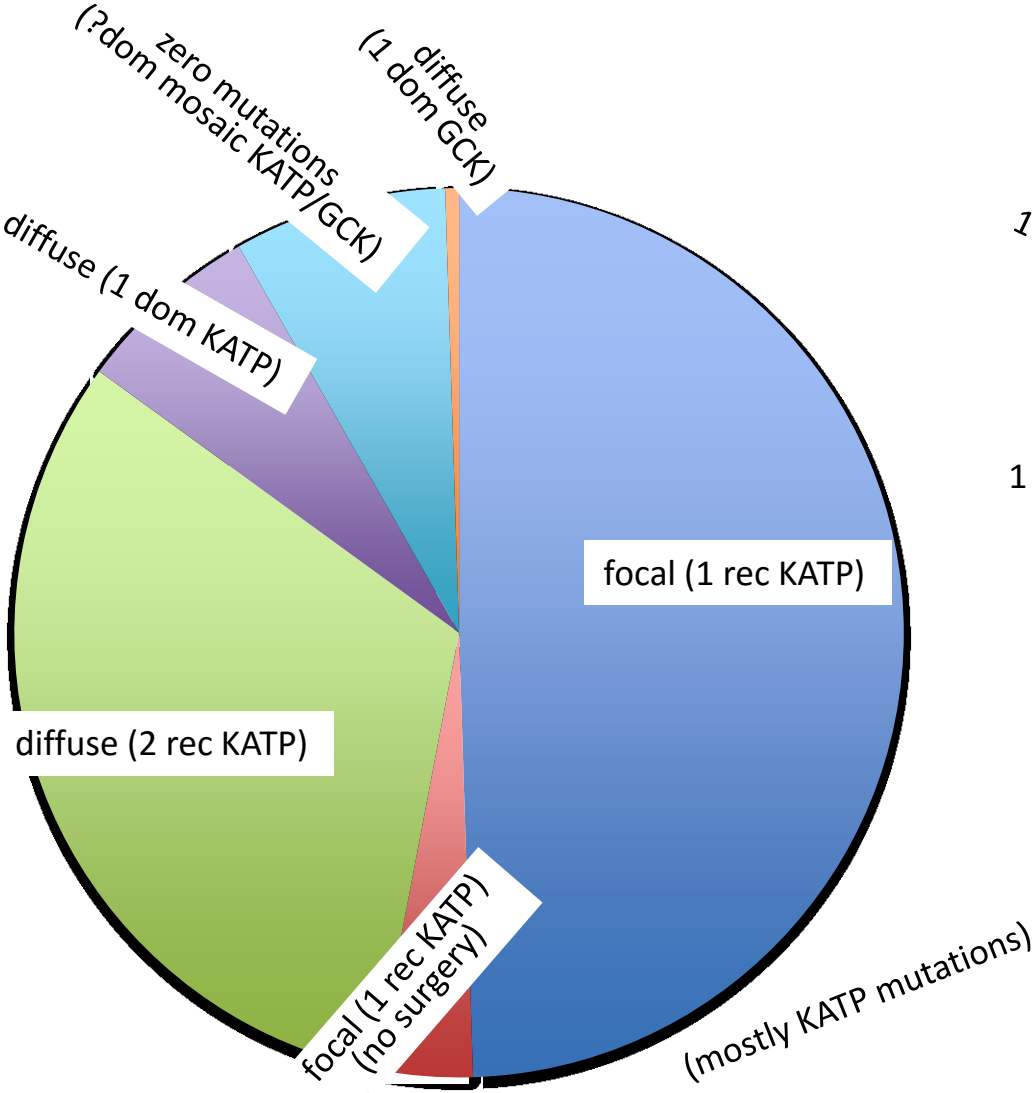
The Children's Hospital *of* Philadelphia®

CONGENITAL
HYPERINSULINISM CENTER

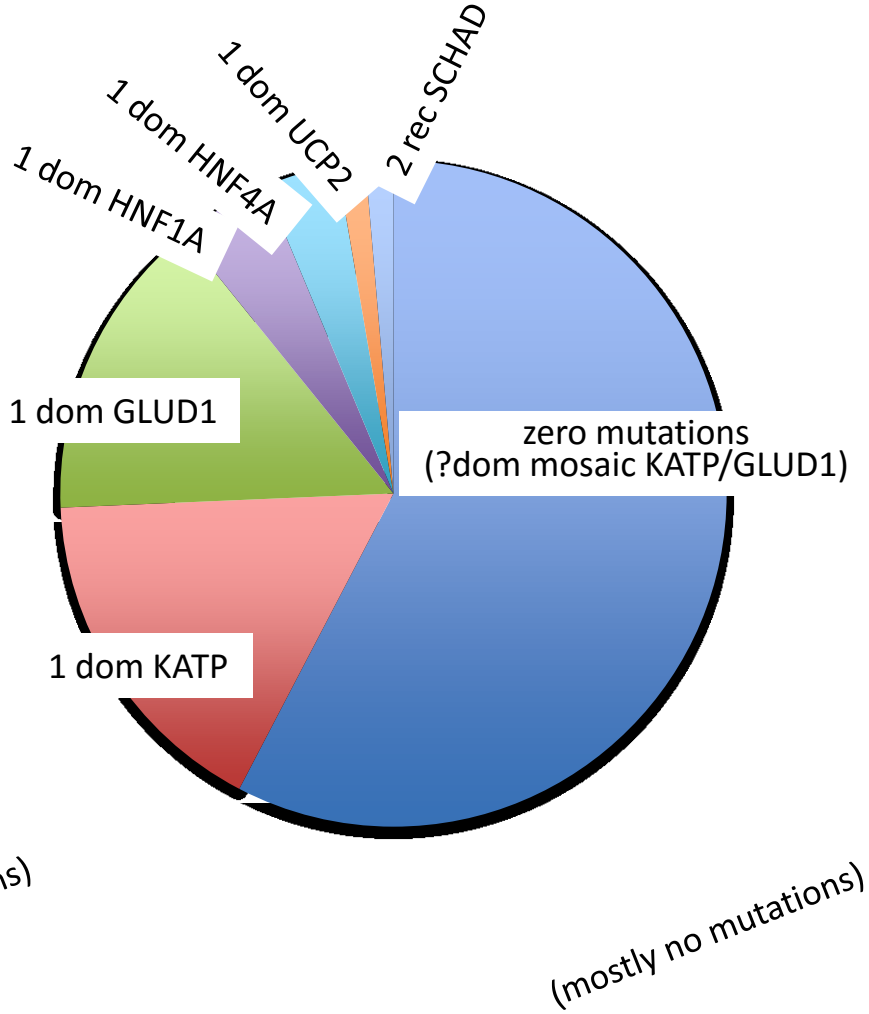
Congenital Hyperinsulinism: Genes



Mutations in 705 Children with Congenital HI (1997-2014)



Diazoxide-Unresponsive
(434)



Diazoxide-Responsive
(219)