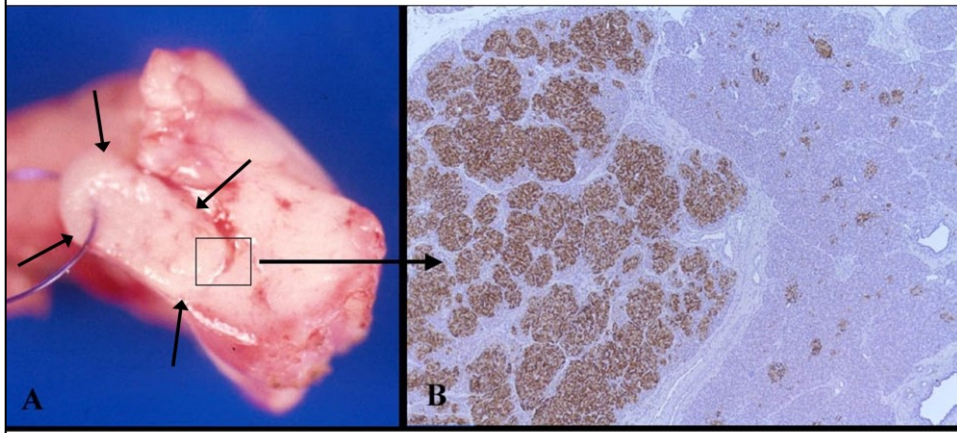
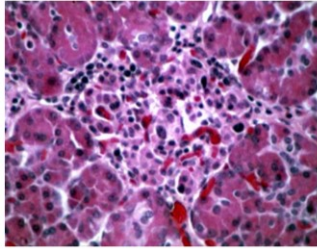


## Partial Pancreatectomy for Focal Hyperinsulinism



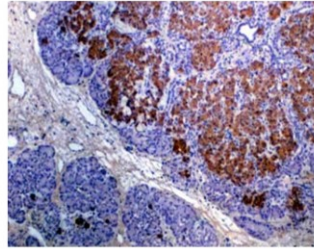
This shows the cut surface of a pancreatectomy specimen through a focal lesion (pointer) causing severe hyperinsulinism in a two week old baby. This 8 X 4 mm lesion is difficult to distinguish from surrounding normal pancreas. Immunolabelling for insulin (brown) highlights the architecture of the focal lesion (left) and adjacent normal pancreas (right).

## Surgical Approach at CHOP



### **Diffuse HI:**

Intraop biopsies (3-5 mm) taken to confirm diffuse disease, then near-total pancreatectomy



### **Focal HI:**

Intraop biopsies taken to confirm focal disease, localize the focal lesion, then **partial** pancreatectomy to completely remove the focal lesion

This shows the surgical approach that we use at the Children's Hospital of Philadelphia since 1998; lessons from the Paris group. For diffuse HI, small intraop biopsies are taken (without use of CAUTERY – pathologists HATE cautery artifact) to confirm diffuse disease, then a near-total pancreatectomy (98%) is performed if the baby is not medically manageable. For focal HI, biopsies are taken to localize the focal lesion, then a partial pancreatectomy is performed to completely remove the focal lesion. **Excellent pediatric pathology is crucial to read the intraoperative frozen sections (2-3 at the microscope).**

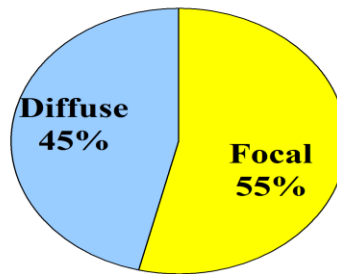
## **PURPOSE**

- Review our experience with pancreatectomy for focal and diffuse HI in 434 patients from 12/1998 to 4/2016 using a multidisciplinary diagnostic and therapeutic approach (endocrinology, radiology, pathology, surgery).
- Susan Becker: evaluate the effectiveness of 18-Fluoro-DOPA PET scan in the localization of focal HI.
- Assess the clinical outcome of partial pancreatectomy in infants with focal HI. Discuss the role of surgery in diffuse HI, LINE, and insulinoma.

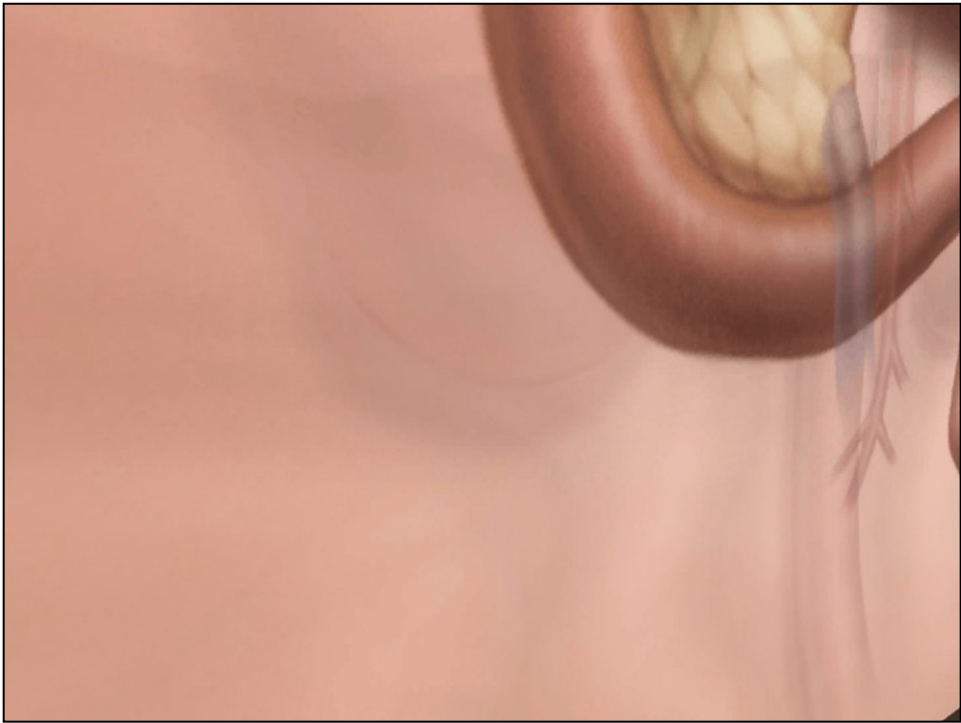
## Prevalence of Focal HI

**434 pancreatectomy patients, 12/98 – 4/16**

**216 Focal**  
**5 Focal/Redo**  
**187 Diffuse**  
**13 LINE**  
**13 Insulinoma**



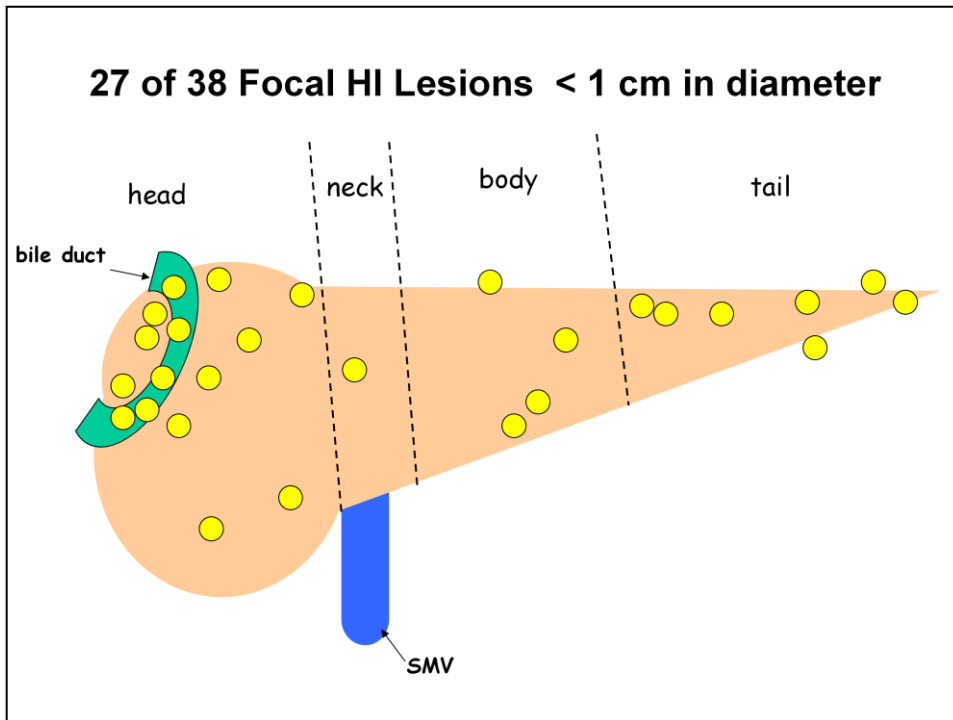
I performed pancreatectomies on 434 patients during the past 17 years. 221 focal lesions include 5 focal/redo cases referred from other hospitals. 187 diffuse cases include some unique HI cases like BWS – Jen Kalish. At the end of this talk, I will briefly discuss surgical aspects of 13 LINE cases = Localized Islet Nuclear enlargement, and 13 insulinoma cases in older children. Parents talk in 2003 – 36 cases.



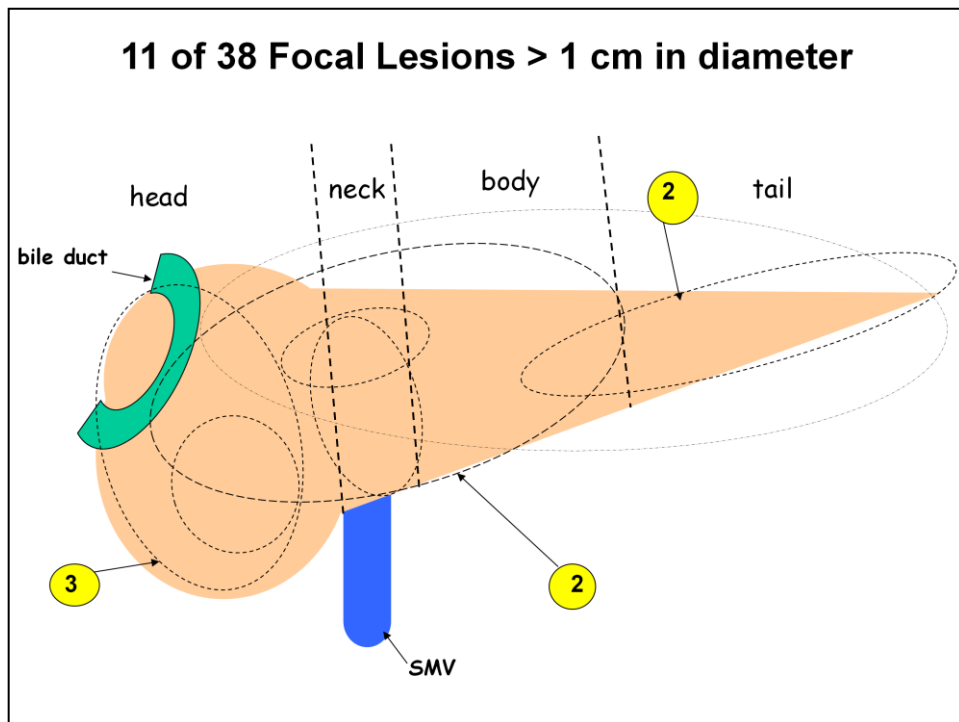
## Partial Pancreatectomy in 221 Cases of Focal HI

- 111 girls, 110 boys. Age at operation: 1 week to 14 months, median age = 7 weeks.
- >2/3rds have visible and/or **palpable** clue for location.
- Spleen preserved in all cases; 1 CBD injury.
- Pancreatectomy extent ranged from 2% to 98%. Vast majority of pancreatectomies were less than 50%.
- 55% of focal lesions involve the pancreatic head/neck; 35 Roux-en-Y operations (28%) including 2 Whipples.
- 5 laparoscopic resections (tail); 1 inadequate resection.
- 97% of focal HI pts cured; virtually all cured past 7 years
- 7 pts require glycemic meds or tube feedings for persistent hypoglycemia. Early lesson = accurate intraop frozen section confirmation of clear margins is imperative.
- No patient is diabetic excluding referred redo patients (total)

Here are the results. There were 111 girls and 110 boys. The age at op ranged from 1 week to 14 months with a median age of 7 weeks. Intraoperative ID was suggested in > 2/3rds of cases by subtle visual clues under loupe magnification or by palpation – became better at this as experience increased. **Palpation is very important (can't do laparoscopically)**. The spleen was preserved in all cases – delicate dissection to preserve the splenic artery and vein. There was one CBD injury: choledochoduodenos. Pancreatectomy ranged from 2% to 98%. The vast majority pancreatectomies were much less than 50%, many 2-10%. 55% of focal lesions involved the pancreatic head/neck. If substantial resection of the pancreatic head required, Roux-en-Y pancreatecticojejunostomy performed to preserve the normal pancreatic body and tail – I will review those cases separately. There were 5 laparoscopic resections for focal lesions in the pancreatic tail; one was inadequately resected and required reoperation. I can preserve more pancreas with an open approach (2% vs 40% or more), no palpation, no U/S for the duct. 97% of focal HI patients were cured; virtually all cured during last 7 years. Seven patients require glycemic medications or tube feedings for persistent hypoglycemia. The lesson is that accurate intraop frozen section confirmation of clear margins is imperative. No patient is diabetic.



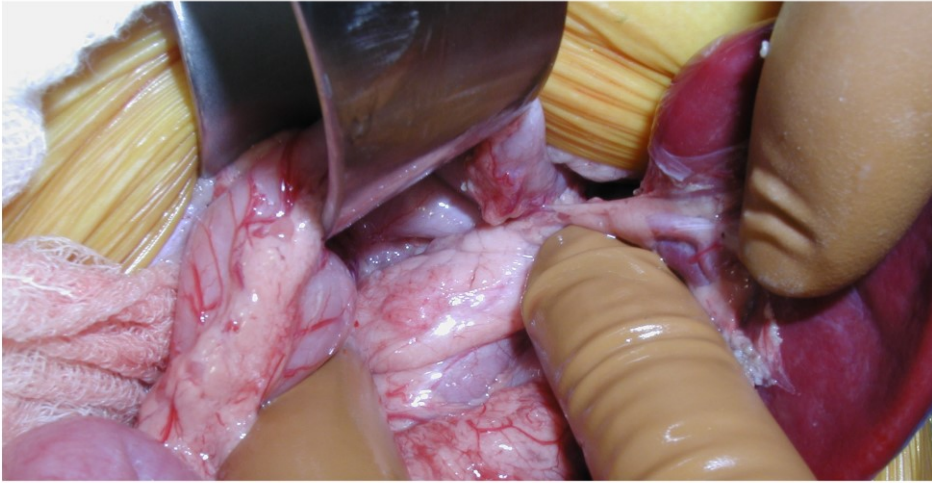
27 of the first 38 focal lesions were 10 mm or less in diameter (as small as 2 mm). 12 of 38 infants had focal lesions that extended into the portion of the pancreatic head that is normally left after a traditional 95% pancreatectomy. Hypoglycemia would persist if that operation was performed.



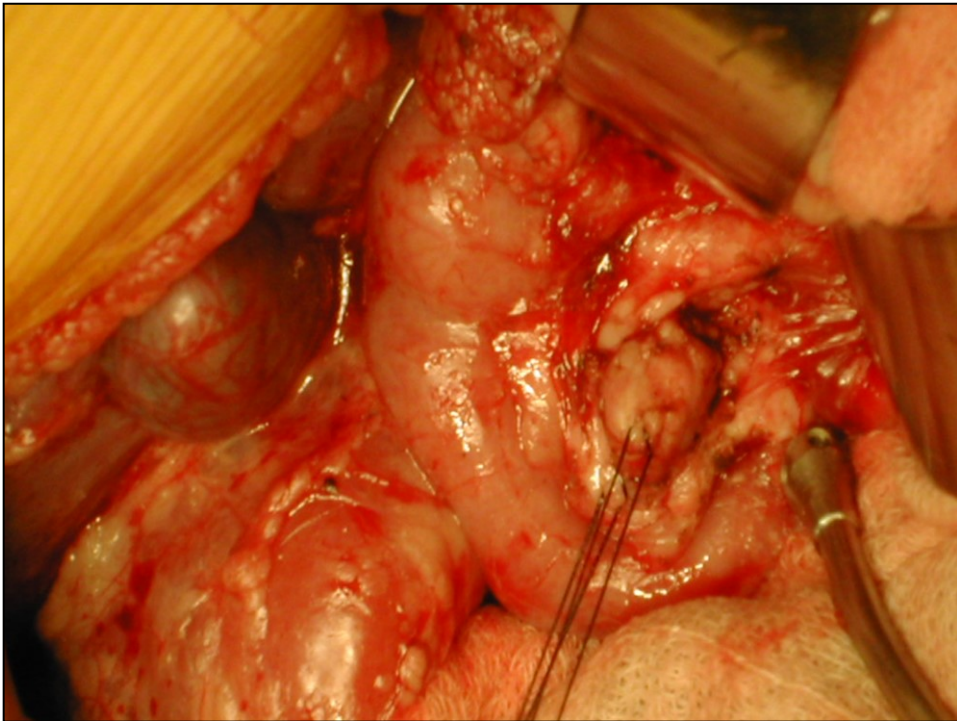
while 11 lesions of the first 38 were larger than 10 mm and a few were much larger. These lesions – large and small - can send out **octopus-like tentacles** so intraoperative determination of free surgical margins is important.

**Excellent pediatric pathology is crucial to read the intraoperative frozen sections.**





Here is an easily visible and large focal lesion on the anterior surface of the pancreatic body.



Here is a large lesion in the pancreatic head that was resected and then a Roux-en-Y pancreaticojejunostomy was performed to preserve the normal pancreatic body and tail.

## **An Important Lesson**

- Three additional patients with focal HI were referred after 95-98% pancreatectomy showed normal pancreas.
- A focal lesion was present in the residual pancreatic head tissue and the lesion was resected.
- One patient from 17 years ago had persistent hypoglycemia treated medically despite complete pancreatectomy and choledochoduodenostomy. Subsequent PET scan showed additional unresected focal lesion within the duodenal wall. He is now diabetic.
- Two patients are insulin-dependent diabetics & require pancreatic enzymes. One of these patients had additional focal lesions in the small bowel.

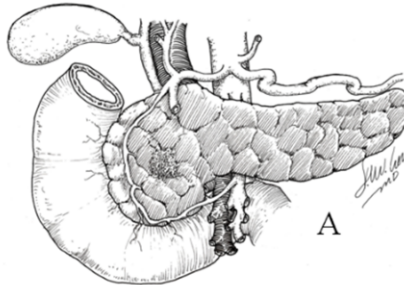
### **Surgical Complications in 221 Focal Lesion Resections**

- Additional resection for residual disease (7 of 8 cured; 4 before and 2 after Roux-en-Y)
- 7 small bowel obstructions (including 5 postoperative SB-to-SB intussusceptions - reduced)
- Chylous ascites (3) – resolved with elemental formula. Ligate lymphatics at base of mesentery. No longer leave drain or use fibrin glue in pancreatic bed.

Here are the surgical complications for pancreatectomy in 221 cases of focal disease. Additional resections – don't give in!

### **Pancreatic Head Resection with Roux-en-Y Pancreaticojejunostomy: Technique**

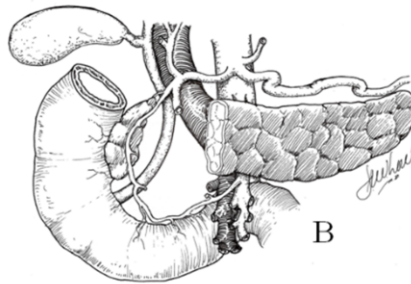
- Transverse supraumbilical laparotomy, Kocher maneuver, expose entire pancreas.
- Inspection / palpation of the entire pancreas, intraoperative biopsies.
- If a large/deep focal lesion is identified in the head of the pancreas a near-total head resection is performed to ensure clear margins by frozen section analysis. Intraop U/S helps judge focal lesion extent and the relationship to the pancreatic and bile ducts.



Mention during the talk that there may be subtle visible or palpable clues for the location of a focal lesion. Intraop ultrasound usually cannot find focal lesions – same echogenicity unless encapsulated (rare) – but can find the pancreatic duct - diameter by U/S is less than 0.5 mm!

## Technique

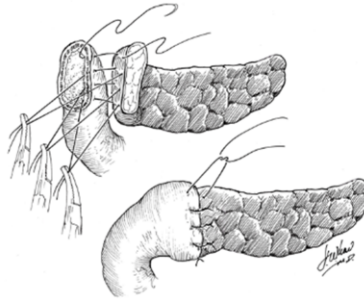
- Common bile duct carefully dissected/skeletonized with blood supply preservation.
- *Gastroduodenal* and *pancreaticoduodenal* arteries and vascular arcade along the duodenum are identified and preserved if possible.
- Pancreatic body transected sharply, no electrocautery. Body & tail preserved.
- A thin strip of pancreatic head is left between the CBD and the duodenal wall.



**Head resection like what is done for a 98% pancreatectomy. ...to preserve duodenal blood supply.**

## Technique

- 25-cm-long Roux-en-Y retrocolic jejunal limb.
- Anastomosis to the *capsule* of the pancreas, *beyond* the cut end; 5-0 monofilament suture. Cut pancreatic end is tucked into the jejunal lumen.
- Posterior aspect first (knots *inside*), anterior aspect last (knots *outside*).
- Interrupted stitches; omentum then wrapped around the anastomosis.



**Skeptics thought this delicate anastomosis could not be done in babies. So much for that.**

## Results

- 35 patients: 19 males, 16 females
- Median *age* at surgery: **8 weeks** (range: 3 to 56)
- Median *weight* at surgery: **5.8 kg** (range: 4.3 to 9.8 kg)
- Mean blood loss: 25 ml (range: 5 to 75 ml)
- One CBD injury: choledochoduodenostomy
- Drains were not used
- Median total OR time: 241 min (\*Biopsies, frozen sections)
- Standardized postop protocol for IV Glucose Infusion Rate

Standardized protocol for postop care including the Glucose Infusion Rate – poster abstract #31 by Natalie Rintoul and our neonatal surgical APNs and HI team.



## Results

- 4 patients had a Roux-en-Y done *after* a previous incomplete focal lesion resection.
- 2 patients had a lesion involving the duodenal wall and required a pylorus-preserving *Whipple* procedure after lesion resection led to duodenal ischemia.



## Results

- One patient developed a 15-cc fluid collection (percutaneously drained)
- Same patient developed SBO 4 months later; exploration/lysis of adhesions.
- *2 reoperations* after the Roux-en-Y due to residual disease in the pancreatic head close to the duodenum. Intraoperative ultrasound was helpful.
- Median hospital stay: 22 days (range 13 to 60)
- 34 out of 35 patients cured of HI
- None have diabetes or pancreatic exocrine insufficiency

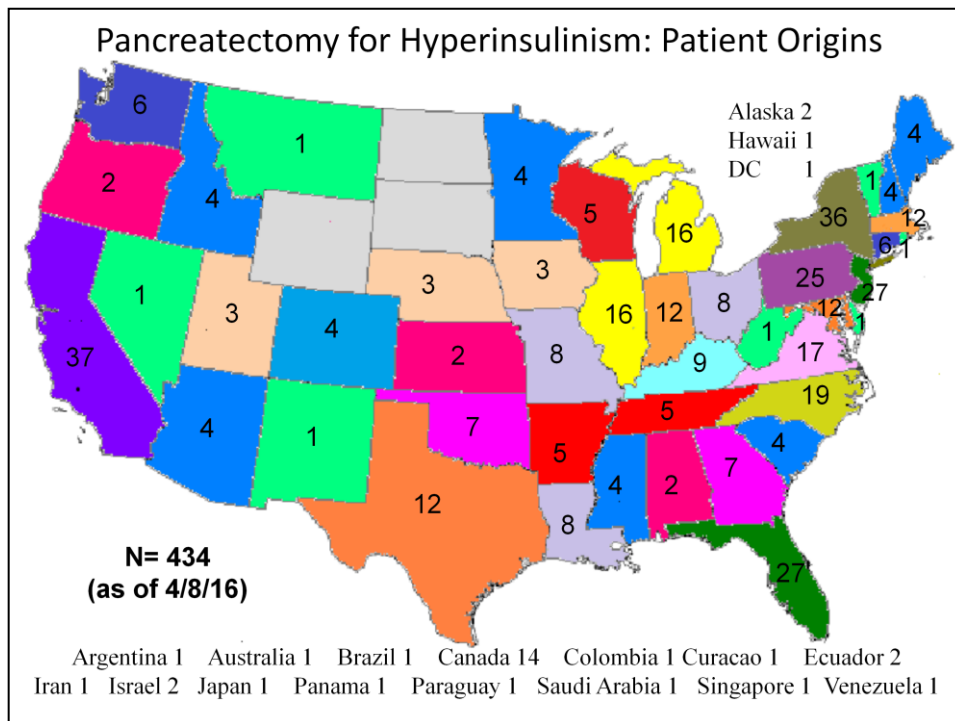
1/35 is not cured – octreotide – probably has focal lesion tissue within the duodenal wall. Only focal lesion baby in past 7 years who was not cured after pancreatectomy. Katherine Lord – the two babies after Whipple both have pancreatic exocrine insufficiency, treated with pancreatic enzymes.

If there is time, mention: A successful clinical outcome is defined as the ability of the infant to eat and fast normally **WITHOUT** glycemic medications, hypoglycemia, or diabetes. **In fact, our endocrinologists require an 18 hour fast without hypoglycemia to qualify for a cure after surgery.**

## Diffuse Disease (187)

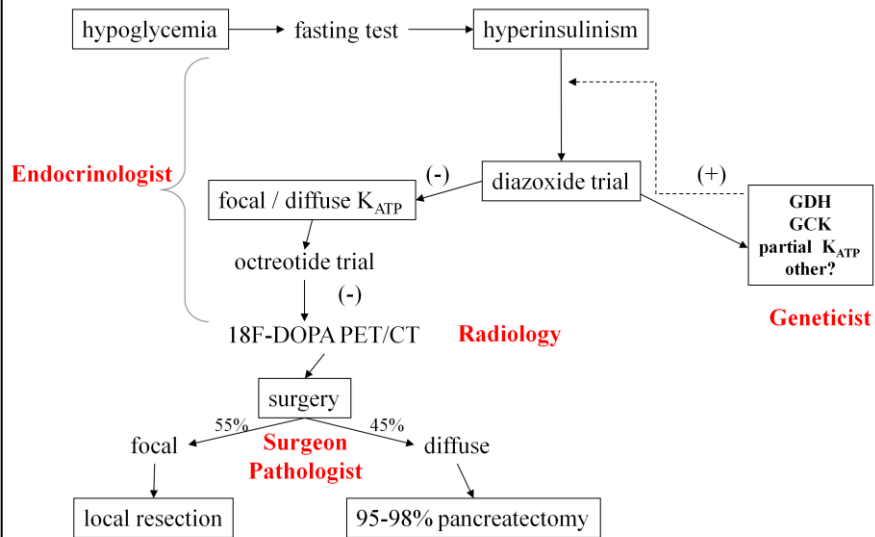
- Surgery = 95-98% pancreatectomy; 13 were biopsies only
- Beckwith-Wiedemann: 13 (60 - 98% pancreatectomy)
- 31% well-controlled; 20% diabetic; 49% required glycemic meds, or 2nd pancreatectomy (9 cases)
- 3 CBD injuries: choledochoduodenostomy (1.6%); no splenectomies
- 1 required resection of distal duodenum (ischemia)
- 1 required IR drainage of intraabdominal collection
- 2 preop deaths due to NEC; 4 postop small bowel obstructions (3 SB-to-SB intussusceptions - reduced)
- Long-term risk of insulin-dependent diabetes
- Surgery is **not** a cure for diffuse disease but can help prevent hypoglycemia and brain damage

BWS – nice abstract #24 about BWS and value of PET scanning by Lisa States, Jen Kalish and others, and Jen Kalish talked about BWS and HI this morning. Tomorrow, Diva DeLeon will discuss the endocrine and neurodevelopmental followup on these patients. The longer the followup – the more diabetes is seen. Rothenberg laparoscopy x 2 cases (entire head remained). Agostino Pierro – unacceptable rate of CBD injury. Outcomes – need new non-surgical solutions.



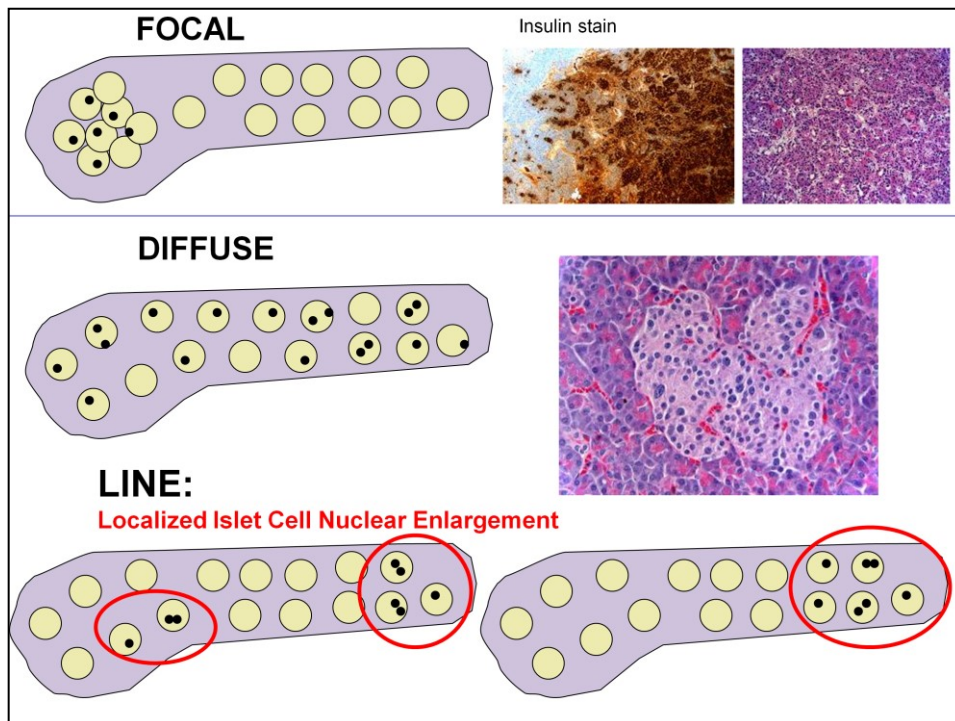
Susan Becker, Enyo Dzata. Wyoming, North Dakota and South Dakota. Very grateful to referring physicians who send their patients to our multidisciplinary HI program: endocrinology, radiology (PET scan), pathology, surgery. >400 pancreatectomies since 1999; by far largest experience in the world. Dragnet. None at Boston Children's Hospital. Many pediatric endocrinologists send their HI neonates here.

## Congenital Hyperinsulinism Paradigm 2016



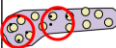
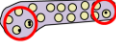
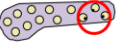
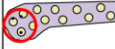
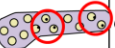

## **CONCLUSION**

A multidisciplinary approach (specialists in pediatric endocrinology, radiology, pathology, and surgery) for patients with the focal form of congenital hyperinsulinism can distinguish focal from diffuse disease, localize focal lesions, and permit partial pancreatectomy with cure in most patients.



Kara Boodhansingh (Bood-hand-sing), Tricia Bhatti, and others from Charlie Stanley's lab. Abstract #21.

## Pathologic characteristics

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6
Pre-op: ASVS or PET scan	Diffuse	Diffuse	Focal	Focal	Diffuse	Diffuse
Frozen sections	21	9	9	9	7	4
Localized Islet Cell Nucleomegaly (LINE)	Head, body 	Head, tail 	Tail 	Head 	Body, tail 	Tail 
% pancreatectomy	95	95	65	50	80	90



## Localized Islet Nuclear Enlargement (LINE)

- A very small percentage of cases of HI that come to surgery do not fall into the focal and diffuse categories
- 13 patients exhibited Localized Islet cell Nuclear Enlargement (LINE)
  - Although histologically this lesion resembles the diffuse form of HI, LINE is distinguished by the regional confinement of nucleomegaly and lack of nuclear enlargement throughout the non-lesional pancreas.
  - Older age at presentation, older age at surgery
  - Good outcome with partial pancreatectomy
  - No  $K_{ATP}$  or other mutations identified
- LINE likely represents a third clinically, histologically, and potentially genetically distinct group of patients with HI.
- These patients may have post-zygotic somatic dominant ABCC8 and GCK mutations in beta-cells in the abnormal regions – great abstract #21 at this meeting

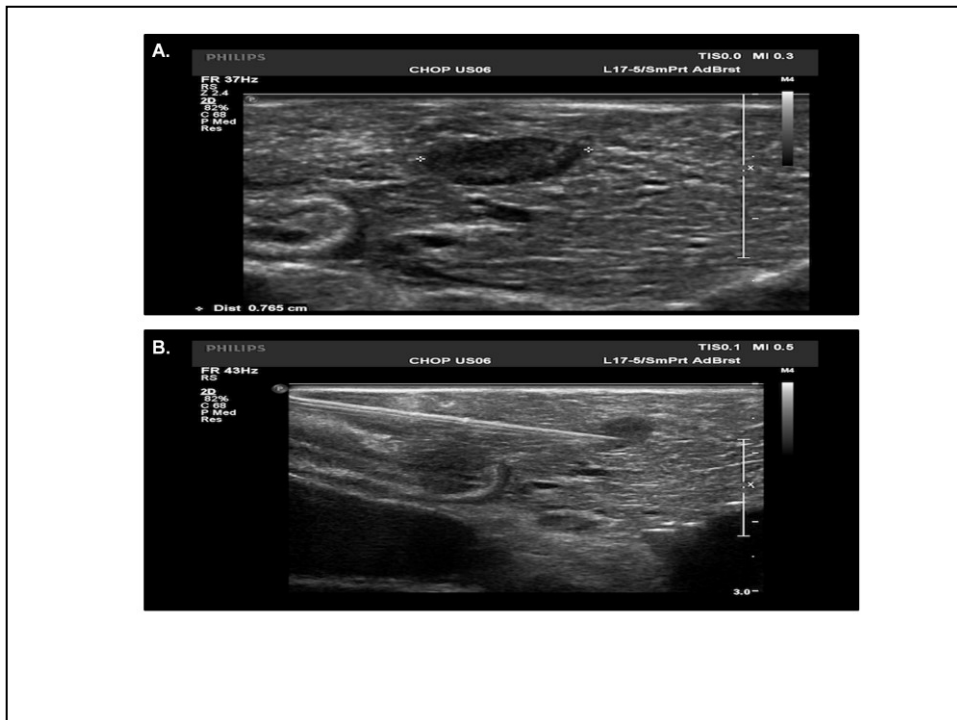
Tricia Bhatti, Kara Boodhansingh, Charlie Stanley and others

<b>INSULINOMA: success of preoperative imaging studies (13 cases)</b>	
<b>Imaging study</b>	<b># successful cases of localization / total # of times study performed</b>
Abdominal U/S	2/10 (20%)
CT	3/12 (25%)
Endoscopic U/S	2/9 (22%)
MRI	5/11 (45%)
Octreotide scan	0/5 (0%)
18F-DOPA PET/CT scan	5/8 (63%)
ASVS	1/2 (50%)
THPVS	1/4 (25%)
ASVS, arterial stimulation with venous sampling; THPVS, transhepatic portal venous sampling	

A retrospective review was performed of patients who underwent surgical management for an insulinoma from 1999 to 2016 (13 cases). Preoperative tumor localization may require many imaging modalities to avoid unsuccessful blind pancreatectomy. Preoperative localization was successful with abdominal ultrasound in only 20%, abdominal CT in 25%. endoscopic ultrasound in 22% (much more successful in adults), or MRI in only 45% of patients, respectively. Octreotide scan was non-diagnostic in 5 patients (persistence -> obstinence). For diagnostic failure, selective utilization of 18-Fluoro-DOPA PET/CT scanning was successful in 63%, arterial stimulation/venous sampling in 50%, or transhepatic portal venous sampling in 25%.

<b>INSULINOMA: Surgical management and postoperative course</b>							
Age	intraop palpation	intraop U/S	tumor location	surgery	lesion size	MEN-1	LOS (days )
4	yes	N/A	head	enucleation	0.7 cm	negative	13
8	yes	N/A	tail	enucleation	1.5 cm	negative	10
9	yes	N/A	head	enucleation	1.5 cm	negative	52
11	yes	N/A	tail	distal panctx	1.5 cm	negative	11
5	yes	N/A	tail	distal panctx	1.2 cm	negative	11
14	yes	yes	neck	enucleation	0.7 cm	negative	17
26	no	yes	3 head/body/ tail adenomas; 2 <sup>nd</sup> op: splenic hilum lesion	distal panctx & enucleations	0.3 – 1.1 cm	positive	67
11	yes	yes	tail	enucleation	1.8 cm	negative	10
9	yes	yes	head	enucleation	1 cm	negative	14

First 9 of 13 insulinoma excisions. All local excisions. Age range from 4-26, median age of 9. Single lesions except in one MEN-1 who had 4 lesions and required 2 operations. All are cured although the MEN-1 patient requires long-term followup.



Unlike focal HI lesions in babies, intraoperative palpation with the assistance of ultrasound offers a reliable method to precisely locate the insulinoma. Intraoperative ultrasound of the pancreas is used to identify a well circumscribed, hypoechoic lesion measuring 0.77 cm (A). Needle localization under intraoperative ultrasound guidance allows for the excision of a lesion that was not easily palpable (B).

