Hypoglycemia

Definition ??

- Because of possible neurologic, intellectual, psychological squeal later on life, many investigators recently, have suggested that hypoglycaemia :
  - In neonates when plasma glucose concentration falls below 40 mg/dl = 2.2 mmol/l
  - In infants or children when plasma glucose concentration falls below 50 mg/dl = 2.7 mmol/l
  - whole blood glucose value is 10- 15% less than plasma glucose

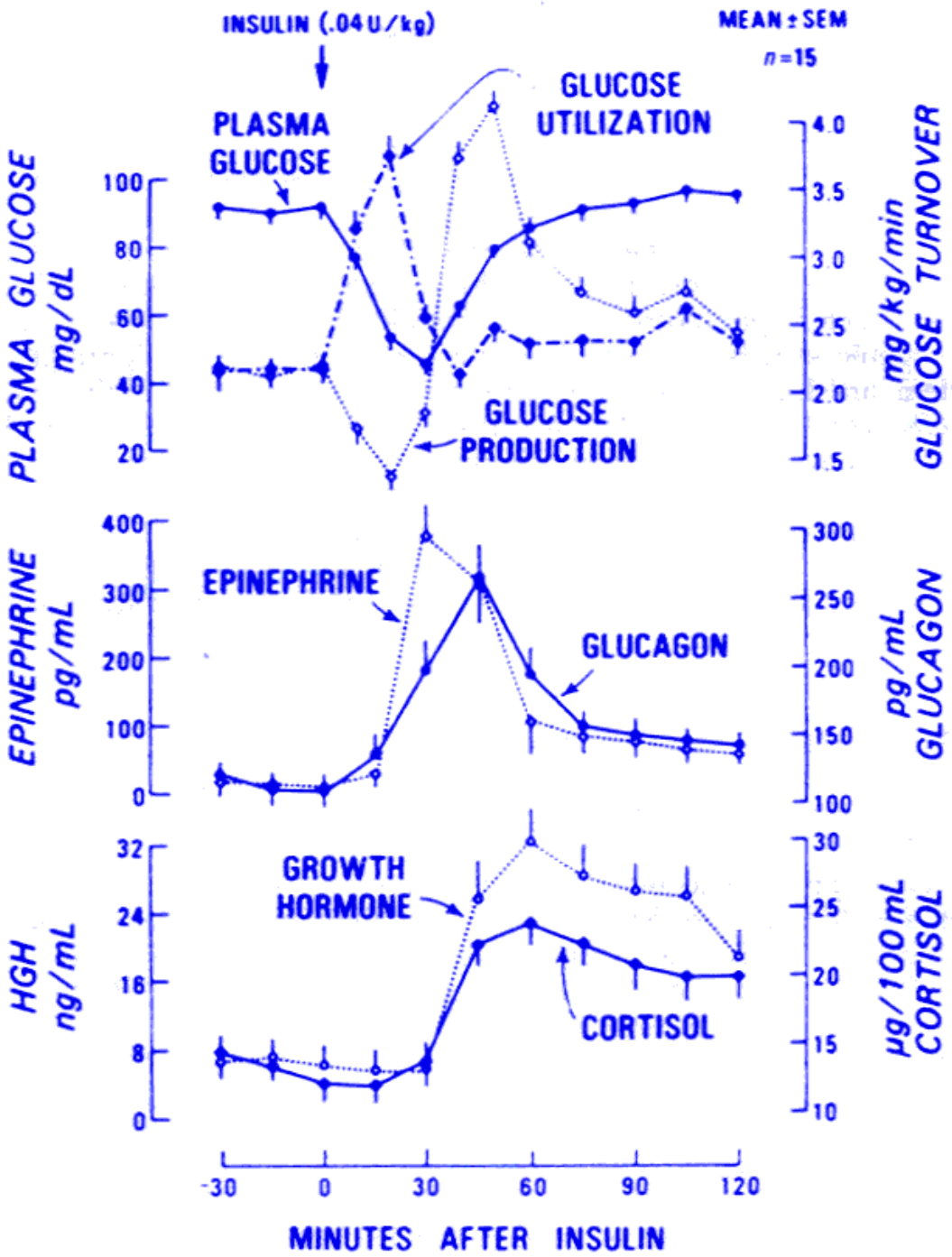
Counter-regulatory hormones

- Rapid acting hormones, are critical for counter regulation of the early phase of hypoglycemia
  - Glucagon
  - Adrenaline

- The absence of the two hormones are not compensated by an even larger response of the other, and more severe hypoglycemia will follow

Counter-regulatory hormones

- Slow – Acting hormones
  - Growth hormone
  - Cortisol
- Their release will be starting 30 minutes post hypoglycemia and their counter –regulatory role is not appreciated until after 3 hours from the onset of hypoglycemia


INSULIN (.04 U/kg)
MEAN ± SEM
n=15
PLASMA GLUCOSE
GLUCOSE UTILIZATION
GLUCOSE PRODUCTION
PLASMA GLUCOSE mg/dL
GLUCOSE TURNOVER mg/kg/min
EPINEPHRINE
GLUCAGON
EPINEPHRINE pg/mL
GLUCAGON pg/mL
GROWTH HORMONE
CORTISOL
HGH ng/mL
CORTISOL µg/100mL
MINUTES AFTER INSULIN

Signs & symptoms

- In neonates (not specific)
  - Lethargy
  - Hypotonia
  - Irritability
  - Feeding difficulties
  - Cyanosis
  - Tachypnea /Apnea
  - Hypothermia
  - Seizure
  - Coma

Signs & symptoms

- In older infants, child and adult
  - Neurogenic (Adrenergic symptoms) are common (first stage symptoms):
    - Sweating
    - Anxiety
    - Tachycardia
    - Weakness
  - Neuroglycopaenic symptoms (become prominent when first stage is not corrected)
    - Headache
    - Irritability
    - Confusion
    - Fatigue
    - Abnormal behavior , amnesia
    - Seizure
    - Coma

How much glucose is needed ?

- The brain of a full term neonate, weighing 3.5kg would require a glucose at rate of 5-7 mg/kg/min.
- Measurement of the endogenous glucose production in infants & young children demonstrate a value of 5-8 mg/kg/min.
- Most of endogenous glucose production in infant & young children can be accounted for brain metabolism
- In adult, brain needs 80% of total glucose production

Hypoglycemia ----- Causes

- Transient neonatal hypoglycemia
  - Prematurity
  - IUGR
  - infant of diabetic mother
  - birth asphyxia
  - polycythaemia
  - Sepsis
  - Infant with erythroblastosis fetalis

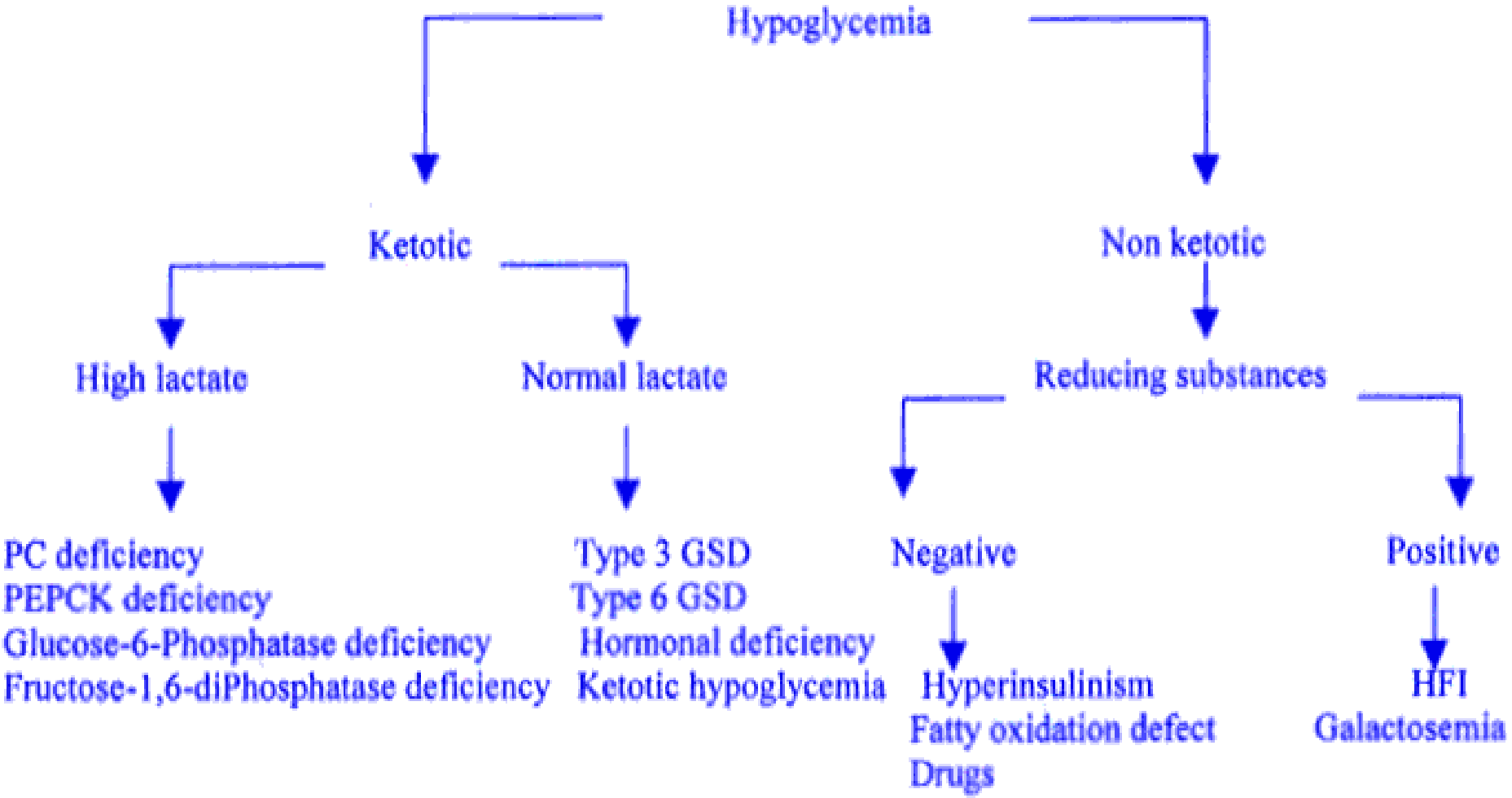
Hypoglycemia ----- Causes

- Persistent hypoglycemia – infantile /childhood
  - PHHI
  - Hormone deficiency
    - Panhypopitutarism
    - Isolated GHD
    - ACTH / Cortisol deficiency
  - Substrate limited
    - Ketotic hypoglycemia
  - Inborn error of metabolism
    - Carbohydrate / amino acids/ organic acids / fatty acids
  - Miscellaneous
    - Drugs, sepsis, liver failure, …..etc.

Diagnostic Approach

- A careful medical history and examination:
  - History of prematurity, IUGR, infant of diabetic mother, birth asphyxia, polycythaemia or sepsis
  - Large baby might suggest Hyperinsulinism
  - Hypoglycemia that is triggered by certain component of diet may be indicative of inborn error of metabolism such as galactosaemia. MSUD,…….etc.
  - Cholestatsis and micropenis occur in setting of Panhypopitutarism
  - Hepatomegaly in glycogen storage disease
  - Myopathy in fatty oxidation defects and in glycogen storage disease

Diagnostic Approach



Diagnostic Approach

- Investigations during hypoglycemic episode:
  - Insulin and C- peptide assay
  - Cortisol
  - GH
  - ketone (β- hydroxybutyrate)
  - Lactate
  - pyruvate
  - Ammonia
  - FFA
  - Urine specimen for:
    - organic acid
    - Ketone
    - Reducing substance

PHHI
Persistent Hyperinsulinemic Hypoglycemia of Infancy

PHHI

- Heterogeneous disorders of glucose metabolism characterized by a combination of hypoglycemia and unregulated high secretions of insulin

PHHI

- Incidence is 1:50,000
- 95% of cases are sporadic
- Rare familial forms are caused by recessive or dominant defects in 4 different genes on 11p15.1
  - Sulphonylurea SUR1 gene
  - Glutamate dehydrogenase (GLUD-1) gene
  - Glucokinase (GK) gene
  - KIR 6.2 : potassium channel inward gene

PHHI

- Chromosome 11p15 containing genes for:
  - » Insulin gene
  - » IGF-2 gene
  - » BWS
  - » Tumor suppressor gene
    - H19
    - P57 KIP 2
  - » SUR1 gene
  - » KIR 6.2 gene
- Some association between Hyperinsulinemia and tumor genesis

Causes of Hyperinsulinism

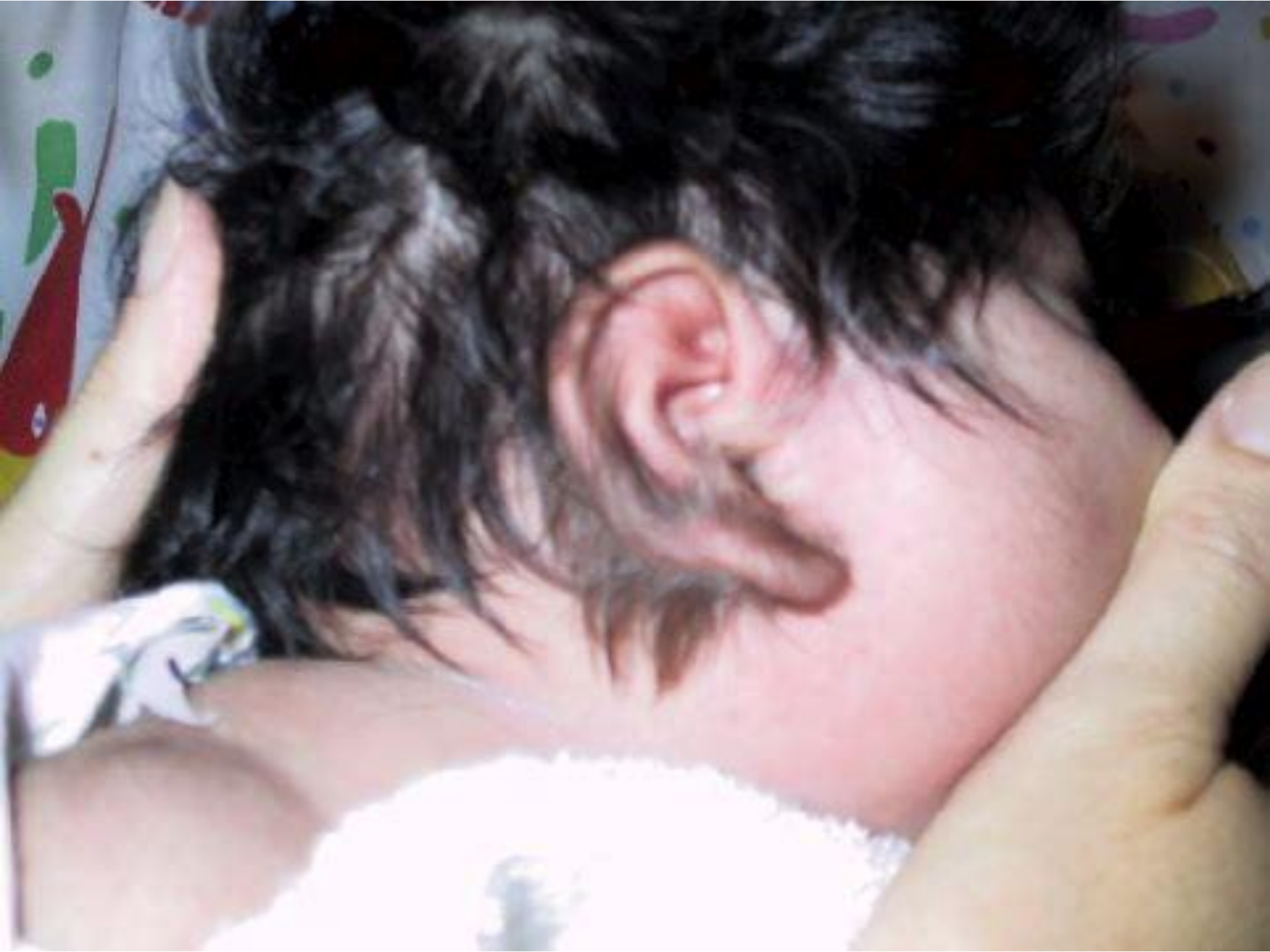
- Transient
  - IUGR
  - Birth asphyxia
  - Erythroblastosis fetalis
  - Beck-Wiedemann syndrome
- Persistent
  - Sporadic
  - Genetic defects of β cell regulation
    - Recessive SUR / Kir 6.2 mutations
    - Dominant Glucokinase enzyme mutation
    - Hyperinsulinism / hyper ammonia syndrome
  - β - cell adenoma
  - Drug –induced
    - Insulin / oral hypoglycemic administration

PHHI

- The most common cause of intractable hypoglycemia in neonatal period and infancy
- In 1934, Graham performed the first successful sub-total pancretectomy for “idiopathic” hypoglycemia in a 14 month old child
- Subsequently, persistent hypoglycemia was referred to the following terms:
  - Nesidioblastosis
  - Islet dysregulation syndrome
  - Persistent Hyperinsulinemic Hypoglycemia of Infancy
  - Lucien sensitive Hyperinsulinism

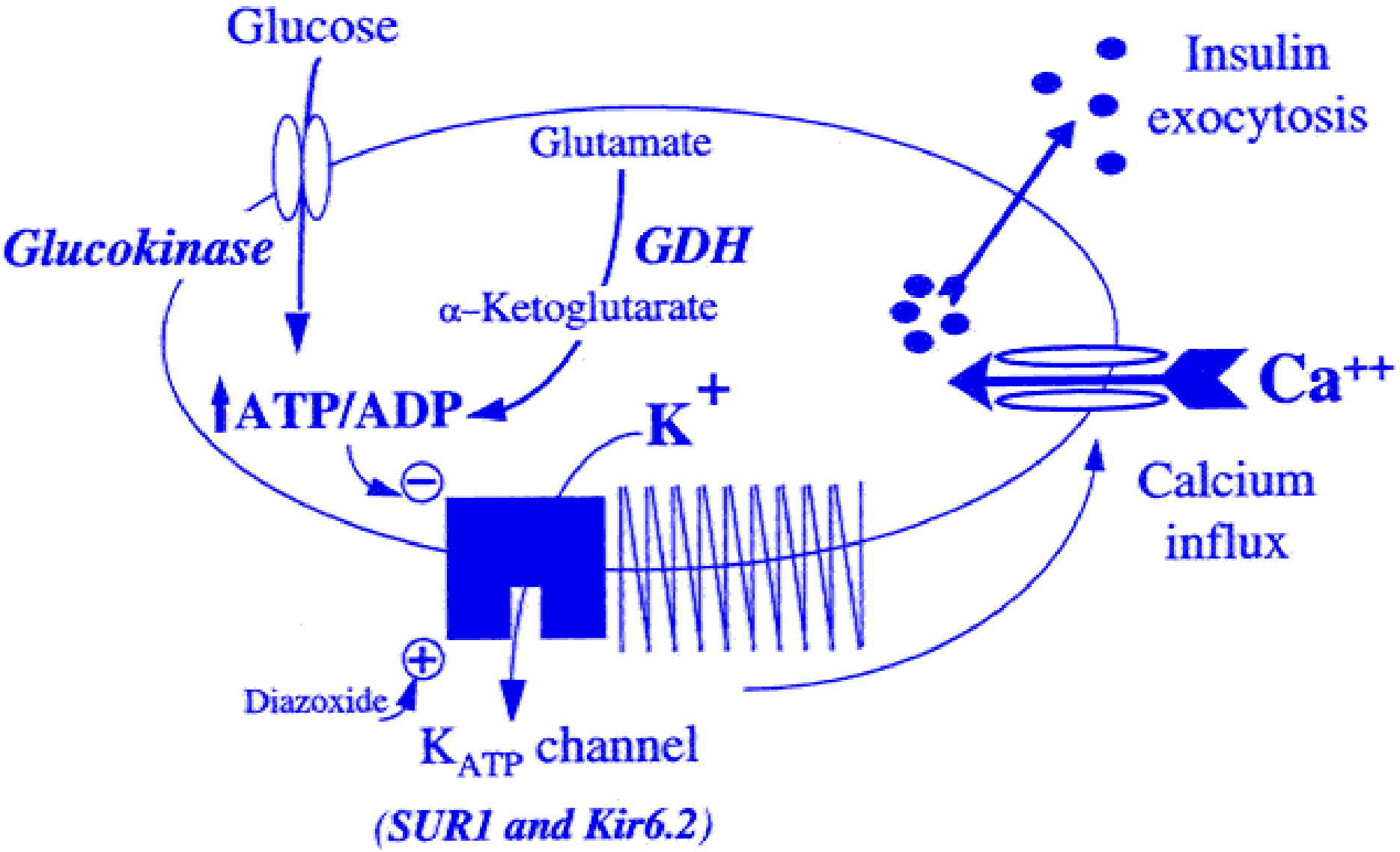
PHHI ---------- Diagnosis

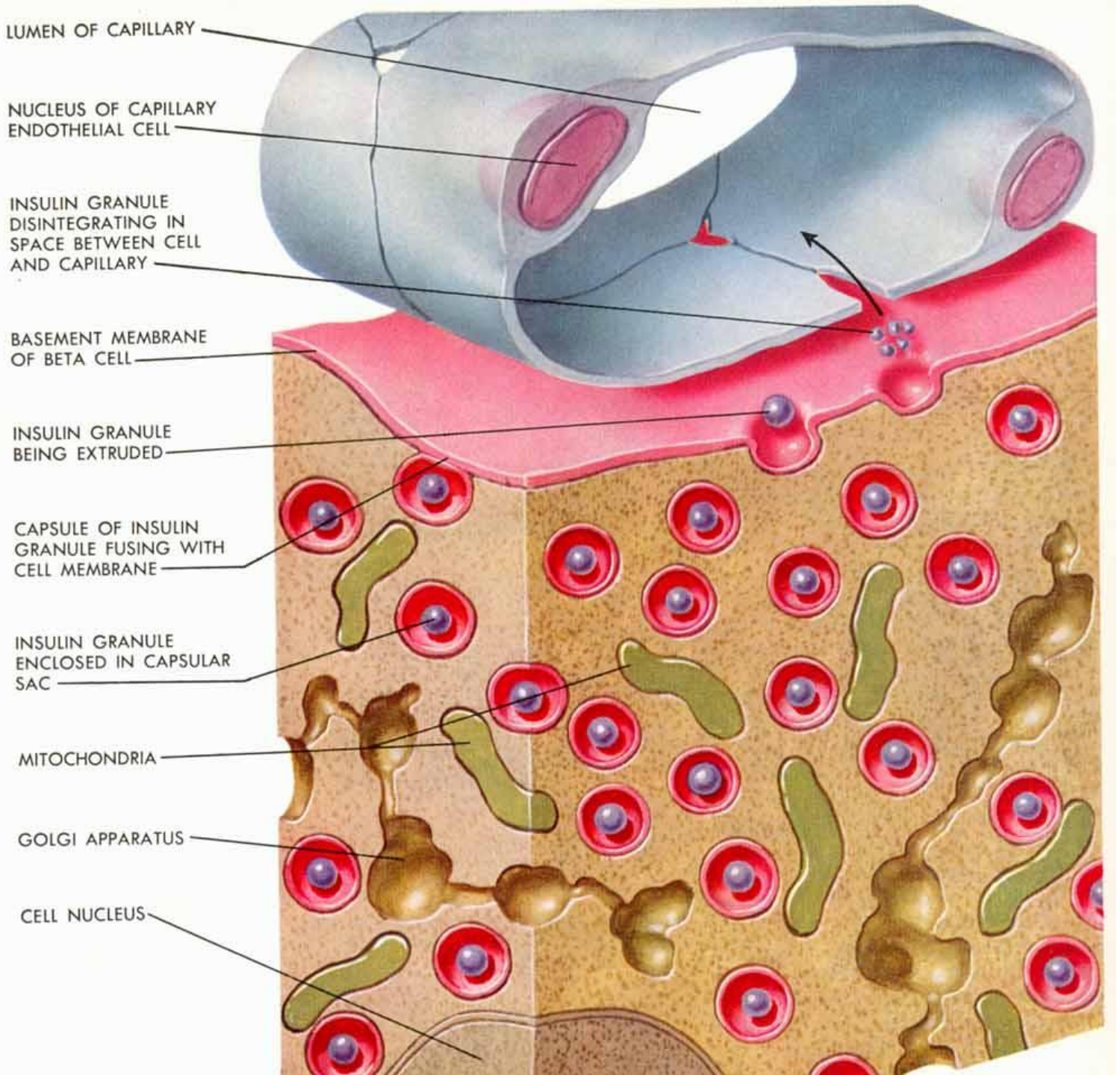
- Large baby
- Exclusion of other causes of transient Hyperinsulinism
- High glucose requirement of > 10 mg/kg/minute
- At the time of hypoglycemia:
  - measurable insulin, pro-insulin and C-peptide levels
  - Low levels of FFA, ketones and IGF-1
  - No metabolic acidosis
  - No reducing substances in the urine
- Rise of blood glucose level of 25 mg/dl or more following Parenteral glucagon administration

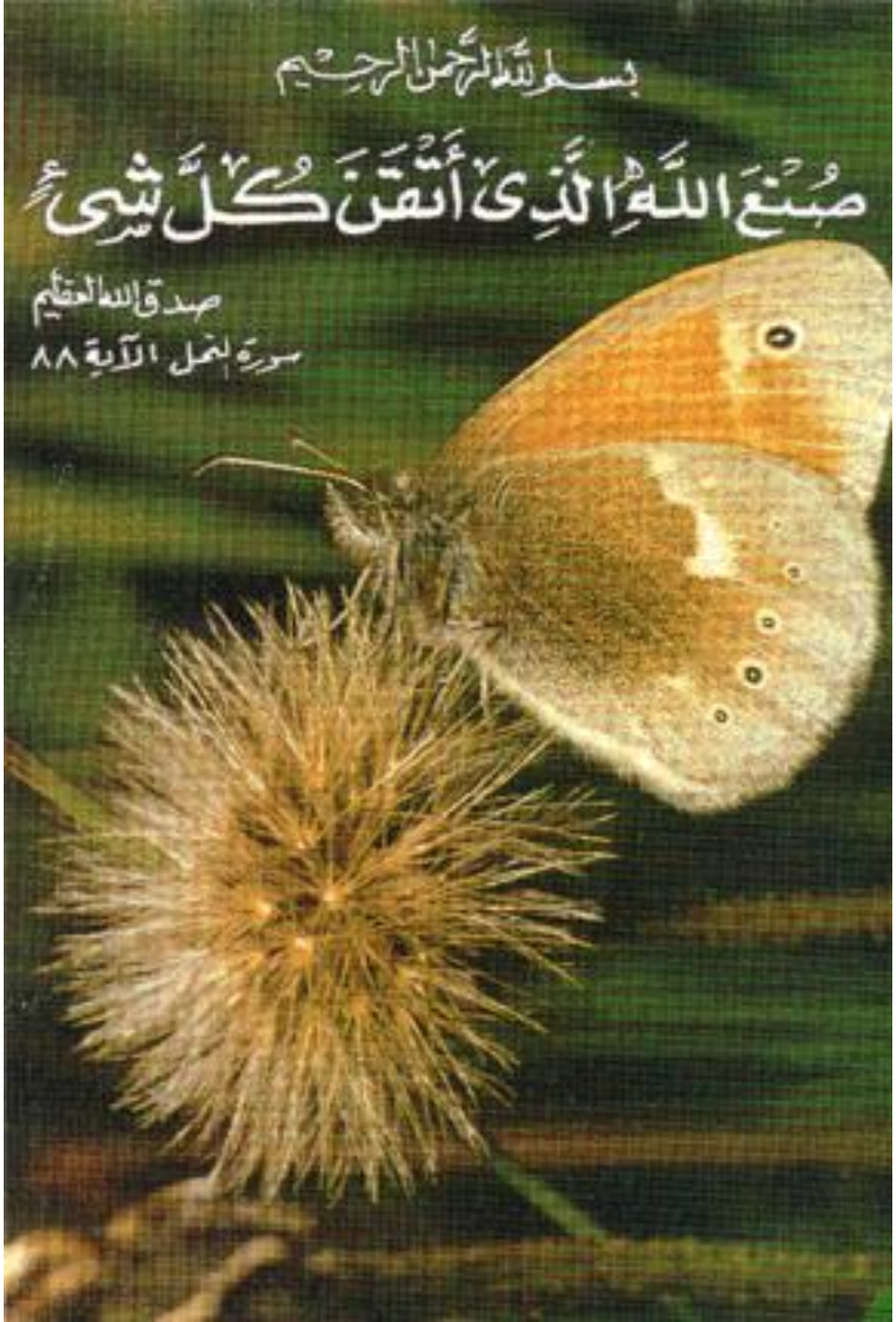


β- Cell regulation of insulin secretion

- Glucose enters the cell via glucose transporter 2 (GLUTR 2) which is not rate limiting for glucose metabolism
- Once inside the cell, glucose is converted to (G_6P) by enzyme Glucokinase (GKS)
- β - cell then metabolizes G_6P to energy
- Increase energy production increases the ratio of ATP to ADP +Pi
- The increased ratio, normally closes the K_{ATP} channel which leads to depolarization of the β - cell plasma membrane, then Ca -channel open
- Increased intracellular Ca, leads to fusion of the insulin containing vesicles and then releasing of insulin


Glucose
Insulin
exocytosis
Glutamate
Glucokinase
GDH
α–Ketoglutarate
ATP/ADP
K+
Ca++
Calcium
influx
Diazoxide
KATP channel
(SUR1 and Kir6.2)


LUMEN OF CAPILLARY
NUCLEUS OF CAPILLARY ENDOTHELIAL CELL
INSULIN GRANULE DISINTEGRATING IN SPACE BETWEEN CELL AND CAPILLARY
BASEMENT MEMBRANE OF BETA CELL
INSULIN GRANULE BEING EXTRUDED
CAPSULE OF INSULIN GRANULE FUSING WITH CELL MEMBRANE
INSULIN GRANULE ENCLOSED IN CAPSULAR SAC
MITOCHONDRIA
GOLGI APPARATUS
CELL NUCLEUS


بسم الله الرحمن الرحيم
صُنْعَ اللَّهِ الَّذِي أَتْقَنَ كُلَّ شَيْءٍ
صدق الله العظيم
سورة النمل الآية ٨٨

β- Cell regulation of insulin secretion

- Glucokinase enzyme (GCK)
  - Gain of function mutations in GCK leads to Hyperinsulinism (AD) form
  - Loss – of – function mutation leads to β-cell insensitivity to extra cellular glucose, with subsequent development of MODY type of diabetes

Genetic form of diffuse Hyperinsulinism

At least 3 forms of congenital Hyperinsulinism have been described

Genetic form of diffuse Hyperinsulinism

- AR Hyperinsulinism
  - This is the most common type
  - Gene defect on chromosome 11 (11 p14-15)
  - representing the most severe type ,usually in the neonatal period with large for date birth size
  - Two component of the pancreatic β - Cell K_{ATP} channel , SUR & Kir 6.2
  - Gain -of- function mutation of these 2 subunits leads to continuous closure of K ATP channel and Hyperinsulinism
  - Because genetic defect in the SUR, diazoxide is usually not effective
  - Infants usually need 95% pancretectomy
  - Because diabetes development in most children who had 95% pancretectomy, some investigators recommend 75% as initial procedure without risk of development of diabetes later
  - Hypoglycemia resolved in 50% of cases with limited resection

SUR & Kir 6.2 mutations

Gene	Mutation*	Location	Predicted Effect	Altered Site	Reference
SUR1	221G→A	Exon 2	R74Q	PstI	29
	375C→G	Exon 3	H125Q	DdeI	29
	560T→A	Exon 4	V187D	Tth111I	33
	563A→G	Exon 4	N188S	TspRI	29
	949delC	Exon 6	317fs/ter	Bsp12861	29
	1216A→G	Exon 8	N406D	XcmI	29
	1630+1g→t	Intron 10	Aberrant splicing	BsrI	29
	1672−20a→g	Intron 11	Aberrant splicing	SpeI	38
	1773C→G	Exon 12	F591L	BsoF1	29
	1893delT	Exon 13	631fs/ter	BstN1	29
	2117−1g→a	Intron 15	Aberrant splicing	PstI	29
	2147G→T	Exon 16	G716V	BbvI	38
	2292−1g→a	Intron 18	Aberrant splicing	BstN1	38
	2860C→T	Exon 24	Q954X	BstN1	29
	3416C→T	Exon 28	T1139M	NlaIII	29
	3644G→A	Exon 29	R1215Q	NciI	29
	3992−9g→a	Intron 32	Aberrant splicing	NciI	29, 31, 39
	3992−3c→g	Intron 32	Aberrant splicing	AvaI	29
	4135G→C	Exon 34	G1379R	EagI	29
	4162delTTC	Exon 34	delF1388	BscRI	29, 31
	4181G→A	Exon 34	R1394H	DraIII	29
	4310G→A	Exon 35	G1400D(23)X†	MspI	8, 29, 39
	4525insCGGCTT	Exon 37	Insertion of AS	PvuII	29
		Exon 37	G1479R		32
Kir6.2	39C→A	—	Y12X	BsaAI	30
	652G→T	—	L147P	PvuI	37

Genetic form of diffuse Hyperinsulinism

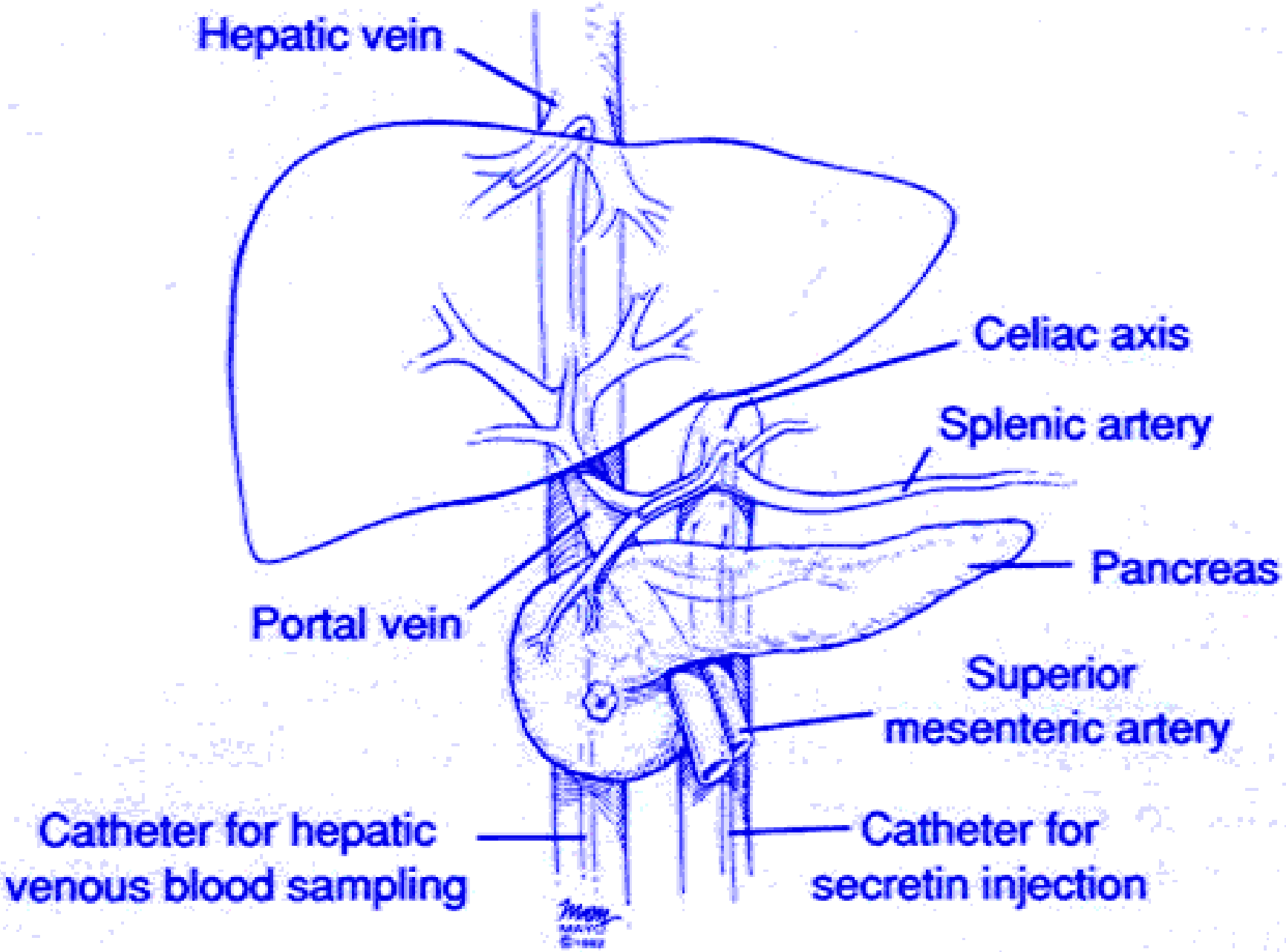
- AD Hyperinsulinism
  - The genetic loci remains unknown
  - Mild form of Hyperinsulinism
  - Due to gain - of -function mutations in GCK (Glucokinase enzyme)
  - different from SUR /Kir 6.2 mutations:
    - very responsive to diazoxide
    - Late sometimes presents as late as adulthood
    - mild presentation
    - Neonates are not usually affected and if so, the are not LGA

Genetic form of diffuse Hyperinsulinism

Hyperinsulinism - hyperammonemia syndrome

- Dominant expressed mutation of mitochondrial glutamate dehydrogenase
- Encoded by GLUD1 gene on chromosome 10
- Excessive activity of glutamate dehydrogenase increases rate of glutamate oxidation, then increasing ATP/ADP ratio which leads to hyperinsulinism
- Persistent mild elevation of blood ammonia to 100 to 200 umol/l (3 - 6 times normal)
- The hyperammonemia seems to be a symptomatic and is not associated with any other abnormalities of amino acid or organic acids found in urea cycle enzyme defects
- These patients may respond to diazoxide or to diet alone

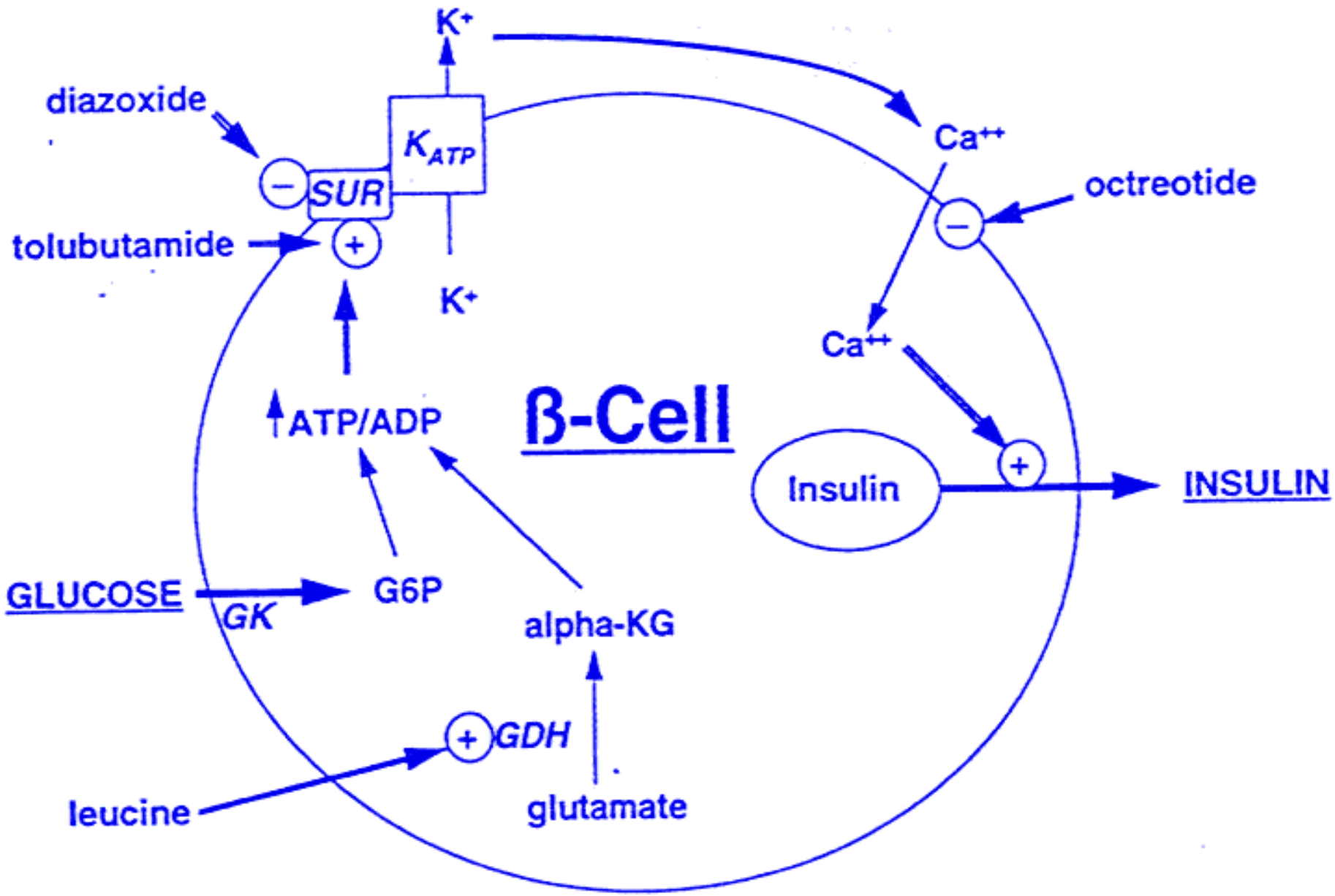
Pre-operative selective venous sampling



Management

- Medical
  - Glucagon infusion
  - Diazoxide
  - Calcium channel blockers
  - Somatostatin analogue
  - Patients with SUR 1 / KIR 6.2 gene mutation usually doesn't respond to Diazoxide
- Surgical
  - Focal adenoma excision
  - 75 % pancretectomy
  - Near-total (95%) pancretectomy

Medical treatment of hyperinsulinism



Management

- Goal of treatment is to achieve safe fasting glucose level
- Diazoxide
  - Acts by inhibiting insulin secretion at SUR1
  - The starting dose is 10 mg/kg, may be increased to 20 mg/kg/day on 3 divided doses
  - Adverse reaction
    - Hypertrichosis
    - Hyperurecemia
    - Salt and water retentions
    - Hyperglycemia and ketoacidosis during illness

Management

- Calcium channel blockers
  - In – Flux of calcium into β-cells is important for insulin exocytosis
  - Nifidipine / verapamil with diazoxide
  - Second line in medical therapy after failing of response to diazoxide
  - High dosed might be needed
  - Hypotension should be avoided
  - Verapamil dose can be up to 3 mg/kg/dose TDS

Management

- Octerotide
  - Long acting Somatostatin
  - Inhibits insulin secretion at the level of calcium channel
  - Doses range from 2 – 40 mcg/kg/day divided into 2-4 doses
  - Adverse effects
    - Nausea
    - Steatorrhea
    - Delayed growth
    - gall stone formation

Thank you